MAY 3 1939

VOL. XXXII. NO. 6 APRIL, 1939

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Section of Dermatology

President—H. Haldin-Davis, F.R.C.S.

[*January* 19, 1939]

Radio-active Ointment as a Method of Surface Radium Therapy

By Albert Eidinow, M.B.

Radon is a gas emitted by radium salts and can be collected in glass capillary tubes. Radon emanation gives off alpha, beta, and gamma rays, and the intensity of radiation can be accurately measured in standard units of millicuries. Radon gas is soluble in oils and in other solvents, but it is rapidly destroyed in air, so that care must be taken in dissolving the gas. It has been shown that the biological effect of the rays of radium, X-rays, and radio-active sources, are 100,000 more powerful than the ultra-violet or the luminous rays of light. Radon continuously emits alpha, beta, and gamma rays, but becomes destroyed so that 50% of energy is lost after four days. The alpha rays are positively charged helium nuclei, they are corpuscular in physical nature, and are rapidly absorbed, causing ionization chemical changes. Clinically alpha rays can only affect the surface layers of the tissue, the power of penetration is small as the rays cannot pass through the thickness of a piece of paper. Air becomes ionized by alpha rays. Thorium X in propyl alcohol has been employed as a source of alpha rays in skin therapy. The beta rays are negatively charged electrons and their power of penetration into the skin is proportional to their wave-length or their velocity. The hard beta rays which pass through a silver screen 0·4 mm. in depth are often employed in surface radiation therapy. Gamma rays are electro-magnetic radiations similar to X-rays.

The radiations of radium, radio-active sources, and X-rays, have been employed in dermatology as they can be absorbed by the skin and cause reaction in the surface or deeper layers of the skin and subcutaneous tissue. The biological action is regulated by the intensity of beta and gamma rays, the period of exposure, the distance of the source from the skin, and the surface area of skin irradiated.

Although the dose of radiation can be accurately measured in terms of standard physical units, individual sensitiveness of the skin may cause irregular reaction. The danger of X-rays and radium in dermatology has been the burning effect with resulting injury which may follow therapeutic radiation. Post-radiation tissue necrosis may cause serious ulceration which will prove very slow in healing and leave a disfiguring painful scar with irregular telangiectases. This was seen in the early days of the surface radium therapy. Later X-rays and radium necrosis may lead to malignant ulceration. Protection by lead and metal screens aims at screening off powerful soft beta radiations which will cause serious skin damage. It was hoped that low-voltage X-rays, known as Grenz or Border rays, would overcome these difficulties, but dosage is troublesome and treatment may cause burning or unpleasant pigmentation.

The use of radium in metal plaques has the disadvantage that the area of skin treated is confined to the shape and size of the plaque, and as a result a defined and regular pattern area is only treated. Radon dissolved in oils and wax makes it possible to use weak doses of beta and gamma rays on an irregular skin area and to apply a uniform dosage to the whole area. S. Lomholt addressed this Section in September 1936 and described his method of using radon dissolved in hard wax. This was

prepared by Dr. Jacobsen in thin plates, 2·0 mm. thick and contained 0·02 mc. to 0·1 mc. or 0·1 mc. to 0·7 mc. per sq. cm. He employed these plaques for the treatment of areas of psoriasis, chronic neuro-dermatitis, keloid or multiple warts, but preferred thorium X in propyl alcohol for cases of hypertrichosis.

In past years I have attempted to treat nævi, ulcers, and telangiectases, following X-rays and radium by intensive local doses of ultra-violet rays. It was only possible to treat superficial lesions which blanched readily with light pressure. The reaction of the skin following radium and X-rays could be more rapidly healed by means of ultra-violet irradiation and, further, the circulation restored. This technique was employed in the treatment of post-radium and X-ray tissue necrosis. The need for measures which would cause reaction deeper in the skin and give greater penetration led to the use of radon dissolved in ointments.

Radon is very soluble in olive oil and petroleum jelly, but the trouble of localizing the ointment and preventing melting and spread over the skin surface has made its application difficult. Efforts were made to stiffen the solvent by means of beeswax, rubber solutions, and paraffin wax. The high temperature of the melting point of many of the wax solvents caused the liberation of fine air bubbles which lost the radon from the wax. Investigations carried out with Dr. W. L. S. Alton and Dr. A. E. Southern at the Radium Institute showed that petroleum jelly was an excellent solvent and less than 10% of energy was lost when radon was dissolved in melted petroleum jelly at 40° C. The use of envelopes made of cellophane solved the problem of the ointment melting and running over the face. The radon gas was dissolved in melted petroleum jelly, poured into the cellophane envelopes and allowed to cool and set. In this way a soft and pliable plaque of radio-active ointment was prepared and could be localized to the area selected for radiation.

Technique of Preparing Radio-active Petroleum Ointment

Petroleum jelly which melts at 37–40° C., is heated over a water-bath and melted. A known volume is measured, i.e. 20 c.c., and poured into a warmed narrow glass vessel. A circular disc is cut out of a piece of fibre 1·0 mm. thick so that it will tightly fit into the bottom of a barrel of a 2·0 c.c. all-glass syringe. The disc is perforated with ten to twelve fine pin-holes. It is inserted into the barrel of the syringe and thrust down to the bottom by the piston. The syringe is warmed and filled with warmed melted petroleum jelly at 40° C. by drawing up the piston. The piston is now removed. A capillary glass tube containing a known intensity of radon, i.e. 20 mc., is picked up with a forceps and placed into the barrel of the syringe. The piston is again inserted and manipulated so that all air bubbles are expelled from the melted jelly. The nozzle of the syringe is thrust deep into the remainder of the melted petroleum jelly in the glass vessel, the piston is thrust down expelling the melted ointment through the perforations of the fibre disc and crushing the glass capillary tube, liberating the radon gas which will rapidly be dissolved. The syringe is rapidly filled and emptied several times, carefully avoiding air bubbles and dissolving and mixing the radon gas with the melted petroleum jelly. In this way 20 mc. of radon is dissolved in 20 c.c. of melted petroleum jelly. 2·0 c.c. of radio-active melted ointment is now measured, drawn up into the syringe, and is poured into an envelope made of cellophane measuring 5 cm. by 5 cm. This is filled to contain 2·0 c.c. of melted radio-active ointment and measures 5 cm. by 2·5 cm. = 12·5 sq. cm. The cellophane envelope containing radio-active petroleum jelly is similar to a radium applicator or plaque emitting beta and gamma rays.

In therapy two intensities are employed :—

(1) 0·5 mc. of radon per c.c. of melted ointment.

(2) 1·0 mc. of radon per c.c. of melted ointment.

The intensity of radiation depends on the quantity of the radon dissolved.

Dr. W. L. S. Alton and Dr. A. E. Southern of the Radium Institute, have kindly

supplied me with measured intensities of radon. They have found that 10% of the energy is lost in the process of the preparation of radio-active ointment. Great care must be taken in handling these plaques. It is advisable to wear rubber gloves when dissolving the radon, and the cellophane plaques should be held with forceps and be well covered so that there is adequate screenage and protection. Radio-active petroleum ointment becomes luminous when seen in the dark; this property of phosphorescence is useful in checking the solution of radon. A cellophane plaque 5 cm. by 2·5 cm. containing radon dissolved in petroleum jelly, 1·0 mc. per c.c., will cause erythema of the normal skin with depilation after forty-eight hours' exposure. The cases treated by this preparation have been (1) congenital nævi, (2) sycosis barbæ, (3) multiple warts, (4) hypertrichosis. Dr. Roy Ward has told me that he has found that cases of nævi at the Radium Institute, which do not blanch readily on pressure with a glass slide, do not respond favourably to radium treatment and are unsuitable. It was decided to treat some such cases. The danger of telangiectases and scarring following the use of radon was discussed, and a few cases were selected and observed for a period of two to three years. Fortunately telangiectasia is extremely rare and severe ulceration or burns have not been observed.

Treatment of Congenital Nævi

The nævi treated were old cases which had had previous treatment, and new cases which did not blanch readily. The area selected for treatment was covered by plaques made of cellophane and filled with radio-active ointment containing 1 mc. per c.c. They were attached by pieces of adhesive strapping and applied for three to four days. A full erythema reaction appeared two to three weeks later. This area was exposed to erythema doses of ultra-violet rays from a quartz vacuum mercury vapour lamp at intervals of fourteen days. Full healing occurred four to six weeks after irradiation. The area becomes paler and it is observed that, on pressure, the blood capillaries will blanch more readily. A second and third application may be applied after an interval of two to three months, but this needs careful observation and control, as often the area will gradually continue to get paler and paler. Radio-active ointment has the advantage that it can be applied to the skin of the irregular contours of the face. Pigmentation rarely follows treatment and, if present, will slowly fade. This appears to be more prevalent during the summer months, and it is of interest to observe that a full erythema dose of ultra-violet rays, causing desquamation of the skin, will diminish the degree of pigmentation.

Telangiectasia

Telangiectases have only followed repeated and intensive doses of radio-active ointment, but are uncommon. Efforts have been made to reduce this by ultra-violet rays. The telangiectases can be destroyed by a molybdenum wire applied to a surgical diathermy electrode. It is necessary to use a local or general anæsthetic. The area is mapped out carefully with the point of the electrode, and as the coagulating current passes slowly over the contours of the telangiectatic blood-vessel this is coagulated and destroyed. Bleeding should be avoided. A dry scab is formed three to four days later, and healing can be accelerated by subsequent use of ultra-violet rays.

Sycosis Barbæ

The results of treatment of sycosis barbæ with radio-active ointment have been most successful. The area of the upper-lip moustache or chin or beard is covered with the cellophane envelopes containing 0·5 mc. of radon per c.c. of ointment, for a period of two to three days. An erythema reaction follows seven to ten days later with œdema. Finally depilation and desquamation will result. The skin area is treated with erythema doses of ultra-violet rays at intervals of seven to ten days. Healing finally results in six to eight weeks.

Warts and Corns

These lesions only need weak doses of radiation, less than the erythema producing doses. A cellophane envelope of radio-active ointment has been applied for twelve hours. Multiple warts have been treated by covering the skin with radio-active ointment and covering the hands with rubber gloves. Little erythema reaction is seen, but the wart slowly disintegrates and disappears. Large flat plantar warts and callosities have responded well.

Hypertrichosis

Cases of hypertrichosis have been difficult. The hair follicles lie deep in the skin structure and heavy dosage of penetrating rays is needed for permanent destruction of the hairs. The erythema reaction caused by radiation lasts for two to three weeks and is distressing to the patient. The cases which have responded best are those in which disfiguring hairs have grown excessively in the later years of life. It is suggested that gamma-ray therapy may be more suitable, although Lomholt advocates Thorium X in propyl alcohol.

Protection

Care must be taken by all who constantly handle and work with radium and radio-active sources. Radon is usually supplied in thin capillary glass tubes. It must always be carried in a proper radon metal carrier and protected with lead covering. The best protection is obtained by distance, i.e. keeping far away as possible from the source of rays. The radon tubes should be handled with fine forceps and never with the fingers, &c. When dissolving radon in ointments and filling the cellophane envelopes a pair of gloves should be worn and the hands should be thoroughly washed directly afterwards. The radon ointment in cellophane envelopes should be used as quickly as possible and, whenever possible, should be held and handled with a pair of forceps. The radon ointment and the plaques should be stowed in a metal-lined box, and when transported should be carried at a safe distance from the body surface. The past experience of the sad tragedies which have followed radium and X-rays therapy make it necessary to take constant and careful precaution.

The following cases were shown by Dr. Eidinow :—

G. P., aged 13 years : Congenital nævus of right side of face. Had had treatment with ultra-violet rays and radium. On November 24, 1937, and February 9, 1938, had treatment with radio-active ointment by means of plaques in cellophane envelopes. Reaction followed. Subsequent treatment with ultra-violet rays. Healed after eight weeks.

W. C., aged 13 years : Congenital nævus of face. Had had treatment with radium and ultra-violet rays. On February 19, 1936, February 9, 1937, and April 1, 1937, had treatment with radio-active ointment by means of plaques in cellophane envelopes. Healed.

E. B., aged 25 years : Sycosis barbæ. Had history of sycosis for one year which had been treated with medicines and ointments. On August 10, 1938, had treatment with radio-active ointment by means of plaques in cellophane envelopes. Reaction followed. Subsequent treatment with ultra-violet rays. Hairs fell out. Healed by September 21, 1938.

R. S., aged 5 years : Congenital nævus of right side of face, which did not blanch on pressure. On June 30, 1937, had treatment with radio-active ointment by means of plaques in cellophane envelopes. Reaction followed with healing. Subsequent treatment with ultra-violet rays.

H. F., aged 40 years : Multiple warts of both hands. Had had treatment with ointments, caustics, medicines, &c., with no success. Subsequently had treatment with ultra-violet rays without success. On May 4, 1938, hands treated by means of radio-active ointment. This was rubbed on for two consecutive nights for twelve hours (twenty-four hours in all) and the hands were covered with rubber gloves. Slight skin reaction and warts gradually disappeared. Free of warts since June 15, 1938.

M. C., aged 5 years : Congenital nævus of right side of face which did not blanch on pressure. On June 26 and November 4, 1936, and on August 11 and November 17, 1937, had treatment

with radio-active ointment by means of plaques in cellophane envelopes. Nævus is paler but telangiectasia has followed.

H. L., aged 37 years: Congenital nævus of forehead, which did not blanch on pressure. Had had previous treatment. Scarring and telangiectases present. On April 7 and August 18, 1937, had treatment with radio-active ointment by means of plaques in cellophane envelopes. Reaction followed treatments. Subsequent treatment with ultra-violet rays. Reaction healed and nævus paler.

J. W., aged 14 years: Extensive "port wine" nævus of left side of face. Had had radium treatment over a period of five years. Has telangiectasia and scarring. Was also treated with ultra-violet rays with little improvement. On March 24, June 2, October 13, and December 8, 1937, was treated by means of radio-active ointment applied in cellophane envelope plaques. Reaction followed with subsequent treatment by ultra-violet rays. Has been healed since February 1938.

A. G., aged 37 years: Congenital nævus of left side of face and neck which did not blanch on pressure. Had had treatment with ultra-violet rays. On February 10, March 24, and June 2, 1937, had treatment with radio-active ointment by means of plaques in cellophane envelopes. Reaction followed with healing. (This patient also had a rodent ulcer over the left temporal area which was treated with radium in 1934.)

Most of the cases shown have had treatment more than one year ago. I selected those treated earliest and watched longest because I was anxious to see whether there was any telangiectasia. The only case in which I saw telangiectasia and which worried me was that of the young child who had a very deep purple-coloured nævus. She had telangiectases on her face, and I made a note on the case-sheets to the effect that I might at some future date try to destroy them by means of diathermy.

Discussion.—The PRESIDENT: We are much obliged to Dr. Eidinow for reading such an interesting paper on a method which will develop and improve. We have all had an opportunity of seeing the results, and I think you will agree with me that the case of sycosis barbæ is a striking success, and that the man who had a nævus on his forehead has been cured with a minimum of residual scarring. I am not so enthusiastic about the cases of the children; the results do not appear to be equal to the others. It is extremely gratifying to the Section that Dr. Eidinow has demonstrated these cases, and of course he is continually striving to improve the method which I am sure will be perfected and prove its utility.

Dr. R. T. BRAIN: I wish to thank Dr. Eidinow for a paper which interested me very much. My first impression was that there is no actual advantage in the vaselin method over the wax method described by Lomholt, for the wax plates could be cut and moulded exactly to cover a lesion and the uniform thickness ensured uniform irradiation. The envelopes of radon in vaselin had the geometric disadvantages of radium plates, and uniform thickness was rather difficult to obtain.

Apart from these conveniences of application, radon has no advantage over radium, and with the latter dosage is much easier to estimate. The old varnished radium plaques were almost as permeable to beta rays as these paraffin mixtures, and Dr. Sequeira and others used plaques for short treatments on a number of skin lesions. It seems rather doubtful whether for a certain dosage a radium plate applied for two hours will have a different effect from a radon appliance applied for two days. In either case, if one succeeds in influencing deep lesions of the skin the ultimate chance of atrophy is considerable.

A further point I wish to raise is whether the suspensions of radon in vaselin are uniform, and has Dr. Eidinow had photographic evidence of this uniformity.

Dr. EIDINOW: We have taken photographic records of these plaques and uniformity is excellent. With ingenuity it is possible to shape these soft little plaques to fit any irregular contour. When I first started I tried to avoid the fixed patterns of the metal plates. I did not hope to get much better results than had been obtained with radium and the plates used at the Radium Institute. A point of interest here is that we have used a very weak source for a long period, i.e. three and a half days. We used 1 mc. per c.c. I think there is a great difference in the biological

action on the skin when taking a plaque and applying it for one hour with high intensity and using a very weak source such as radio-active ointment for a long period of time.

Dr. SEMON: While commending the results obtained in the vascular nævi I am impelled to sound a note of warning against using any form of radiotherapy in the treatment of hypertrichosis. I hold that it is not possible to destroy the hair follicle without at the same time causing serious and progressive damage to all the other constituents of the skin. I would go further and state my conviction that the epilation which normally follows an erythema dose of X-rays is not evidence of special hypersensitivity of hair bulbs, but merely a sign that a certain dose had been administered. I consider, therefore, that such treatment has been based on a false deduction and never could succeed. This afternoon I have seen a case of widespread and most disfiguring telangiectasia of the face and neck following X-ray treatment for hypertrichosis some three years previously. I believe no woman who has undergone the heavy dosage employed by the firm responsible in this case, would entirely escape the development of stigmata at some time in her subsequent history. I fervently hope that such methods as radon pastes or wax plaques will never become available for use by the unqualified operator.

The PRESIDENT: I think Dr. Eidinow was very cautious in what he said, and he was not anxious to take over the treatment of hypertrichosis. I have had an opportunity of reading his paper and he was careful to say that this method has only a limited field of application in hypertrichosis.

Superficial Ulcerated Squamous-celled Carcinoma on Bridge of Nose.—G. B. MITCHELL HEGGS, M.D.

Patient, W., woman, aged 34.

Previous history.—Fell on to the kerb about twenty-two years ago and has since had a scar on the nose.

Present condition.—There is a rather unusual spreading ulcer on the bridge of the nose. Around it the skin is white and telangiectatic, and the ulcerated area appears to be on the lowest point of this peculiar patch; one segment of the edge of one of the ulcers resembles a rodent.

Biopsy report (Professor W. D. Newcomb): "Squamous-celled carcinoma of skin. It is only moderately keratinized but mitotic figures are scarce. The growth extends to base of piece removed.

Discussion.—Dr. J. H. TWISTON DAVIES: I saw a case like this a few years ago. There was a basal-celled epithelioma nearly 10 sq. cm. in area occupying a large part of the surface of the nose. The only indication of its presence was the appearance of occasional bullæ which were diagnosed by myself and another member of this Section variously as herpes simplex and impetigo, although we were both aware that she had previously had an epithelioma. Later, when the patch of alleged impetigo would not heal, I made a diagnosis of artefact, and even went to the length of taking her into a nursing home and having her psycho-analysed. Finally when a new lesion appeared under an occlusive dressing, I made a biopsy, and only then did I discover that there was an epithelioma. The epithelioma, which was an ordinary basal-celled growth, did very well with radon seeds. The resulting scar, though most people would call it a good one, is much easier to see than the original epithelioma was.

Dr. I. MUENDE: I am reluctant to express a definite opinion on the van Gieson section, but my impression was that we are dealing with a basal-celled epithelioma of the rare spindle-celled type. This would tally with the clinical appearances which are those of a superficial benign basal-celled epithelioma.

Dr. W. N. GOLDSMITH: I would like to support that. I have seen several cases of even frank prickle-celled carcinomas yield beautifully to X-ray treatment.

Dr. MITCHELL HEGGS: That is the view, founded on general pathology, of Professor Newcomb, and that was really why I changed my method of treatment. I shall go into the matter again in view of the encouraging remarks on radium therapy in this sort of case made by most of the members of the Section. Dr. O'Donovan told me that he and Dr. Sequeira had had two such

cases, if not more, of the same sort at the London Hospital, of which he had shown two here: (1) A girl aged 24, *Brit. J. Dermat.*, 1923, **35**, 70. (2) A girl aged 21, *Brit. J. Dermat.*, 1923, **35**, 334. The title he had used was carcinoma faciei apud puellam. The treatment arranged at the moment is removal and skin graft by Professor Pannett.

Grouped Miliary Sarcoid of Boeck.—LOUIS FORMAN, M.D.

E. H., female, aged 47.

History.—Rash appeared in December 1938, quite suddenly. A few small lesions have developed since. Health has been quite good. She had had a cold a month before the eruption appeared.

Present condition.—Large, circinate, erythematous patches on the medial aspect of the left arm, and similar ones on the right arm, on the legs below the knees, and on the back. On the border of the patch are numbers of brownish papules, and within are other brownish papules. Early lesions on the back are seen to be composed of three or four brownish papules. There is a little erythematous mottling of the breasts. No enlarged glands. No enlargement of the spleen.

Tuberculin test (1/50 bovine and human) strongly positive.

Wassermann reaction negative.

Skiagrams—Chest: Emphysematous. Increased shadowing suggests chronic bronchitis. No evidence of phthisis. Bones: No abnormality of hands, wrists or lower forearms.

Report on section from edge of lesion on back (Dr. I. Muende): "The epidermis is unaltered and throughout the corium there are small, circumscribed masses of endothelial cells with practically no lymphoid cells. In one of the deeper and younger lesions there is a peripheral zone of lymphoid cells."

Dr. C. H. WHITTLE: I showed a case not really like this in general appearance, though histologically there was a distinct resemblance. The lesions were scattered about and came out quite suddenly as an eruption as in Dr. Forman's case. They were not circinate, and did not produce such a picture as in Dr. Forman's case, but the lesions individually were similar, and histologically as far as I could see, they were identical with those in my case. The Section then agreed that my case was of the Boeck sarcoid type, but a point I want to make is that I showed this section to Dr. Whitfield who would not accept the diagnosis. He maintained and continued to maintain, when he had examined the section more carefully at home, that this was not a sarcoid at all, but that it was really a neoplastic condition.

Angioma Serpiginosum.—W. N. GOLDSMITH, M.D.

M. M., female, aged 20; shorthand-typist.

Present condition.—On the inner aspect of the right lower limb are numerous punctate telangiectases arranged in clusters and curved streaks. There are also a few telangiectases on some fingers of the left hand and on the left forearm. The lesions do not entirely disappear on diascopy.

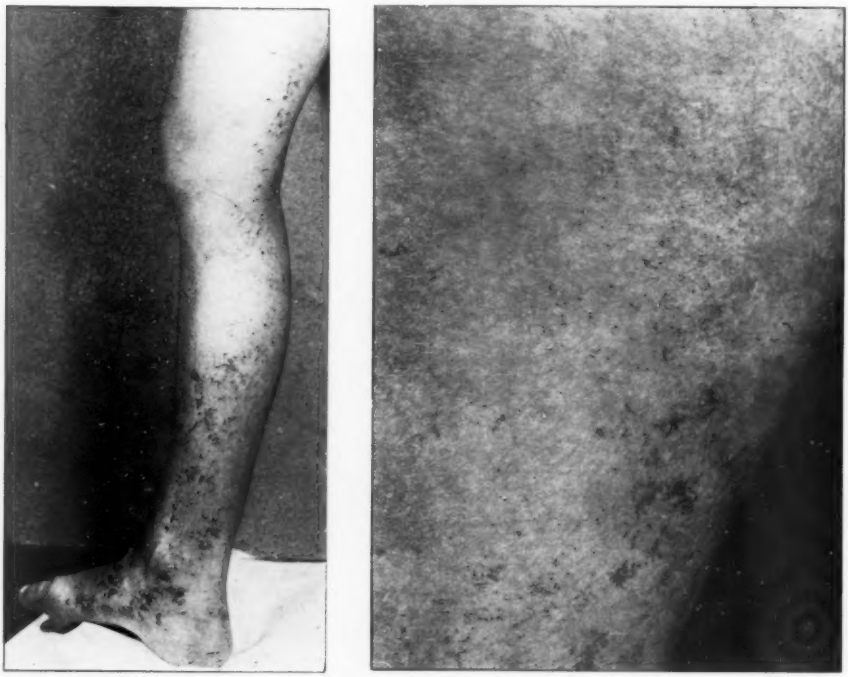
On the thigh are some round dusky areas which represent the remains of reaction to the Kromayer lamp. Within these areas the telangiectases have disappeared. Similarly treated areas on the lower part of the leg, however, still show the presence of the lesions.

History.—Duration thirteen years. It began at the bottom of the right leg and gradually spread upwards. None of the original lesions has disappeared spontaneously. The spots on the left upper limb began two years ago.

Histology (Dr. W. Freudenthal).—A portion of skin from the right ankle showed a number of newly formed small blood-vessels with thick walls.

Comment.—In Continental literature there is still confusion between angioma serpiginosum and Schamberg's disease. A case like this is, I feel, convincing that the

two conditions are quite distinct. The distribution is suggestive of a systematized angiomatous nævus.



Dr. Goldsmith's case of angioma serpiginosum.

As treatment with the Kromayer lamp is not being completely successful I shall try Grenz-rays.

Discussion.—Dr. F. PARKES WEBER: We must be grateful to Dr. Goldsmith for having brought up such a splendid example of a condition the very existence of which has been called in question, although it was originally described in England so strikingly by Sir Jonathan Hutchinson. In the present case the lesions really are telangiectatic; without any pigmentation; they temporarily disappear completely with ordinary finger-pressure.

One of the difficulties in discussing this condition is the terminology. *Angioma serpiginosum* is a term which does very well for the gyrate streaks, but for diffused areas of the condition it is somewhat confusing. I feel sure that the condition sometimes occurs over diffuse areas, for instance, over part of the back and abdomen. The minute constituent lesion, the red spot, is a telangiectasis, not an angioma, and it is not always grouped in serpiginous lines. Therefore I suggest that the condition should be called *miliary telangiectasia*. To this term one can add the words: *in straight or serpiginous lines* or *streaks, in small clusters*, or *in large diffuse areas*.

Conditions such as that under discussion are what I should call "developmental"; that is to say, they have developed either *in utero* or there is a potentiality at birth which leads to their development later on. As far as I can make out there is no familial or hereditary incidence recorded in any of these cases, which indicates that they cannot potentially have been present

in the fertilized ovum. Something happens at an early stage of intra-uterine development, which leads to their development either before birth or sooner or later after birth.

Dr. SILCOCK: What dosage of Grenz-rays does Dr. Goldsmith propose to use if he treats angioma serpiginosum by that means, and at what intervals? Also what total dosage would he give?

Dr. W. N. GOLDSMITH: I was interested in what Dr. Parkes Weber had to tell us with regard to hereditary features of angioma serpiginosum. I agree with him that the name is not entirely happy. I, too, have seen a similar condition over the chest, in which there was not any serpiginous arrangement but which I think was, nevertheless, the same disorder.

As to the dosage of Grenz-rays I would start with 800 r at intervals of about a month.

Case of Erythema Annulare Centrifugum.—W. N. GOLDSMITH, M.D.

M. D., female, aged 52.

History.—She first saw me on November 7, 1938, with an oval marginate eruption about 2 in. in its long diameter on the right shoulder. The border was very narrow, red, and very slightly scaly. Within it the skin was normal except for a slight brownish discoloration. At the exact centre was a little raised papule like a mole. It had been present for two or three months and had started with the central spot, which she called a wart, around which the skin had become red and scaly.

She had been attending Dr. Bernard Hart for an anxiety state and had been taking bromide. Scattered over the trunk were some discrete papulo-pustules characteristic of a bromide eruption.

I felt sure it must be tinea circinata, but was a little puzzled by the central papule. I could, however, find no fungus in scrapings. Moreover, it was quite uninfluenced by Whitfield's ointment and by fuchsin paint. During this trial period it did, however, vary in intensity but was not obviously spreading. On one occasion she said she had noticed a smaller ring concentric with the first which travelled outwards and fused with the first.

Biopsy: The central nodule and a portion of the ring were excised and examined by Dr. Freudenthal. The central nodule proved to be not a mole and probably not an infective wart. There were acanthosis and downward epidermal processes and some inflammatory exudate. The portion from the ring showed only very slight inflammatory changes.

Since the biopsy, though most of the lesion had faded, there has been a further outward spread at some portions of the ring, especially downwards and medially.

Comment.—Dr. Freudenthal, who wrote a paper on this subject in 1928 (*Arch. für Derm. und Syph.*, 154, 581) suggested that it might be a variety of erythema migrans (Lipschütz). It certainly appears to be some kind of erythema perstans. The two varieties which stand out most distinctly are erythema migrans of Lipschütz and erythema annulare centrifugum of Darier. Many varieties have been described by different authors which do not quite fit either of these. This case differs from Darier's variety in being solitary and much slower in evolution. It differs from Lipschütz's variety in that the latter is still more rapid in its evolution, tending to cover a large area of the body, and has a much more prominent margin. On the other hand it resembles some of Lipschütz's cases in having a central papule. In some of Lipschütz's cases he established that the central papule was caused by the bite of Ixodes. It seems likely that a bite of some kind may have been responsible in this case.

Discussion.—Dr. J. T. INGRAM: Does Dr. Goldsmith think this might not be a case of neurodermatitis (lichen simplex) aggravated by treatment?

Dr. GOLDSMITH: I do not think it is a neurodermatitis. There has been no itching and it was distinctly annular. It has only a short history.

Apyrexial Ulceration, Lung Abscess and Pyæmia.—A. C. ROXBURGH, M.D.

Mrs. J. H., aged 52, married. Patient of Dr. Ernst of Romford.

History.—August 1936 : She first noticed what she thought was a gnat bite on the dorsum of the left foot (there is, however, no definite proof that it was a gnat bite). This broke down into an ulcer and became painful and daily larger. First seen by Dr. Ernst eighteen days after onset ; there was then an acute ulcer on the dorsum of the left foot, circular in shape and about 2 in. in diameter with a yellow slough all round the edge. The floor of the ulcer was covered with bright red granulations and there was a thin serous discharge exuding from under the edges which were raised, congested and undermined, and separated from the sloughing area by a network of peculiar small linear hæmorrhages. The whole lesion was exquisitely tender and surrounded by an area of intense inflammation.

These appearances are described in detail because they are typical of every subsequent lesion of more than a few days old. There were no enlarged glands in the groin, the patient felt well in herself, and it was thought to be just an infected gnat bite which had been neglected. Local antiseptic applications were therefore first applied. Eusol, flavin, dettol, and hydrarg. perchlor. were tried in succession, but in spite of these the ulcer continued to grow in a very characteristic manner. The yellow slough separated, but the next day another ring of epidermis ¼–½ in. wide would be seen to be sloughing, again surrounded by the peculiar little hæmorrhages already described. In twenty-four hours this too would separate, but the process repeated itself again and again, the ulcer consequently enlarging by steps of ¼–½ in. every second day. Clearly the inflammatory process was spreading in the deep layers of the dermis, and the cutting-off of the blood supply to the more superficial layers caused the sloughing. A culture of the discharge at this stage, three weeks after the onset, gave a pure growth of hæmolytic staphylococcus arranged in tetrads.

She was seen by Dr. Hugh Gordon who was doing my work, and in view of the above it was thought that it might be an anaerobic infection and H_2O_2 by continuous drip through Carrell's tubes was administered to provide nascent O_2. N.A.B. was given intravenously, although the W.R. was negative. There was no change, and one week later she was seen by me. The ulcer had now assumed alarming proportions, it covered the whole of the dorsum of the left foot and ankle, and was beginning to invade the sole. The actual ulcer was surrounded by a yellow slough 1 in. wide, and beyond this was a bright red band 1–1½ in. wide. I drew Dr. Ernst's attention to its resemblance to the acute spreading gangrene of the skin sometimes seen on the abdomen after appendicectomy, and suggested that circumvallation by diathermy should be tried as spreading gangrene of the skin can usually be stopped in this way. This was carried out by Dr. Ernst on the same day, and in addition the whole edge of the ulcer was excised, and with a swab the whole of the granulations were wiped away. They proved to be about ½ in. thick and of a soft, thick porridgy consistency. When this had been done it was found that all the superficial vessels, nerves, and tendon sheaths, stood out like a dissection. At this time there was also a small similar lesion over the left lower ribs in front and two indolent-looking lesions on the scalp.

The foot began to improve at once and small healthy granulations covered the floor of the ulcer. Every few days, however, a small spot or two at the edge would be found to have become swollen, and unless promptly cleared out with a small Volkmann's spoon and the overhanging edges cut away, the same process of spread promptly reasserted itself. After three doses of N.A.B. she got severe reactions and N.A.B. was discontinued, but four blood transfusions of 250 c.c. each were given from two of her sons who had recently recovered from scarlet fever.

Nothing except daily dressings with spirit and ether and clearing out of extensions as necessary seemed to do any good. These were carried out under gas. After five weeks the condition of the foot had improved to a considerable extent and a Thiersch

graft from the right thigh was done to cover the very large denuded area. These all took well and healed up rapidly, but unfortunately the thigh area where the graft was removed showed signs of disease. Anti-staphylococcal serum was now given in view of the hæmolytic staphylococcus found originally, but again without obvious benefit. The patient eventually healed and was able to leave hospital in December 1936. She was quite healed at the end of February 1937 (six months after the onset). Apparently a small part of the thigh wound broke down again some two weeks later, but as it was very small and only an occasional bead of pus exuded, the patient did not think anything of it and went about her ordinary active life for a year. In February 1938 she felt a sudden pain in the left side of the chest which became persistent, and when seen twenty-four hours later all the signs of a left lower lobar pneumonia were present with pleurisy and blood-stained sputum. There was no dyspnœa and only a mild rise of temperature (T. 99° F., pulse 80). The sputum in three days became thick and purulent, and six days later she began to develop crops of typical pustules on the arms, trunk, and scalp. Skiagrams of the chest were taken and she was seen by Dr. Clifford Hoyle, of Brompton Chest Hospital. He agreed that the condition was probably an embolism into the lung from the still active focus on the right thigh, and that a lung abscess plus subacute pyæmia were now present. He suggested the possibility of a coccidioidal infection but no confirmation of this has been found. The patient was admitted to hospital and all the cutaneous lesions excised as they occurred. Some were excised complete for section and bacteriological examination by Professor Garrod, Dr. Oliver, and Dr. Francis. Sputum and blood were likewise investigated with the following results :—

Pathological Reports

February 12, 1938 : A small lump of excised tissue composed of indurated skin covering a small abscess situated in the subcutaneous fat. Abscess opened aseptically and pus examined. No evidence of *Coccidioides immitis* or tubercle bacilli. Hæmolytic *Staphylococcus aureus* in pure culture. No fungus on Sabouraud's medium.

February 14, 1938 : Examination repeated on another excised subcutaneous abscess showed complete absence of bacteria and culture sterile. Leishman films from pus showed rather a large number of eosinophils. Material injected into a rabbit without effect. Blood cultures aerobic and anaerobic and in 10% CO_2 sterile after three days. White blood-count and differential normal.

Histology of skin nodule (section shown).—Showed area of necrosis in dermis heavily infiltrated with polymorph leucocytes. Immediately deep to this a thrombosed vessel with wall considerably disorganized. Appearances suggest that lesion is due to an embolus.

February 12, 1938 : Sputum.—Blood-stained mucopus. Almost complete absence of organisms. No tubercle bacilli found. No growth of any organisms of pathological significance. A mouse died as result of inoculation, but no pathogenic organisms found in heart blood or peritoneal washings.

A noteworthy feature of the case has been that in spite of the severity of the attack (she was in hospital for three months), the constitutional disturbance has been singularly small. Apart from anxiety, depression, and a mild feeling of malaise, there has been a striking absence of toxic phenomena. No pyrexia, appetite good, bowels regular. Nor have there been any signs of embolism elsewhere in the body except the skin. No splenic pain, no albuminuria. Blood-count normal.

The lymphatic glands have never been enlarged even when many ulcers were present.

All the skin lesions ultimately healed and repeated skiagrams (exhibited) show that the lung lesion is slowly clearing up although there is still a large opacity in the left lower lobe. The sputum, however, has remained purulent and occasionally blood stained.

The patient has remained well except for a solitary recurrence on the foot in October 1938. It was thought that tropical experts might help, and a specimen of pus and sputum was sent to Dr. Martin at the Tropical Hospital, but unfortunately the material was too heavily contaminated.

The present trouble began with signs of activity in the lung fourteen days ago, when she noticed that the sputum was blood stained. One week ago a lump appeared on the dorsum of the right foot at a place she had bruised a month earlier. There is now an infiltrated lesion 1·25 cm. in diameter consisting of an ulcer with a central slough and violet overhanging edges. There is also a small boil-like lesion on the right side of the nape of the neck, present five days.

The patient has had about 120 gas anæsthetics, has been seen by a number of consultants, and has had a large variety of treatments, but no convincing evidence of the nature of the infecting organisms has so far been obtained, because the hæmolytic *Staphylococcus aureus* which has been found several times is regarded by the pathologists as probably a secondary invader, and no tubercle bacilli, actinomycosis, or other fungus, has ever been seen and the patient has had practically no fever.

Discussion.—Dr. G. W. BAMBER: In November 1934 I showed a case (male) before this Section with lesions similar to those on the feet of Dr. Roxburgh's case. I described the case as one of pseudoblastomycosis from which nothing but *Staphylococcus aureus* was recovered. The man was treated with staphylococcal toxoid. Treatment took about two months, after which the condition completely cleared.

Dr. PARKES WEBER said he thought that the original condition was due to local infection of the skin with spreading phagedænatous ulceration (a less acute form of "spreading gangrene of the skin"). Vaccine treatment in such cases must be waste of time, and Dr. Roxburgh had introduced the correct radical treatment. In spite of the appearance of the lesion in the lung (whatever its nature was), the patient's general health seemed to be improving, and fresh lesions in the skin would have to be dealt with radically, as they appeared.

Dr. I. MUENDE: Dr. Roxburgh's case brought to my mind a case which I saw in Vienna about ten years ago, and proved to be due to infection with the avian type of tubercle bacillus which gives rise to very acute necrosis. Has a tuberculin test been done in this case? (Dr. Roxburgh: No.) In such cases the Mantoux reaction made with avian tuberculin is usually very strongly positive.

Dr. HEGGS: Dr. Muende's remarks call to my mind a case we had at St. Mary's which is extraordinarily similar to Dr. Roxburgh's. A woman came up from Hillingdon with a septic lupus on the side of her face for treatment at St. Mary's. The usual investigations were made and treatment started. She would not come up for treatment regularly. We offered to pay her fare and even to house her near the hospital, but she would not go on with the treatment. We lost sight of her for about eighteen months, and then she turned up with ulcers such as Dr. Roxburgh has described, which were obviously growing rapidly. X-ray of the lung showed a picture similar to that which we have seen, only rather more suggestive of tubercle with calcification. After a number of sputum tests we managed to get a positive one. She had an ulcer on her wrist which exposed all the tendons, and she had several lesions on the buttocks which looked as though they might penetrate to the bony pelvis.

In the local treatment we had most success with prontosil ointment applied locally and with injections of various varieties of chaulmugra oil. Unfortunately, the patient has discharged herself from St. Mary's, improved but not cured.

Dr. I. MUENDE: Dr. Heggs' case is now under my care at Redhill. She had an enormous ulcerated growth on her neck and since she was admitted several new acute, rapidly spreading necrotic lesions have appeared on the left thigh. Her Wassermann was supposed to have been positive at one time, but is now negative. I gave her N.A.B. and thyroid, but although the scalp lesion responded rather dramatically, those on the thigh were uninfluenced.

Cultural examination of the ulcerating lesions produced growths of a diphtheroid bacillus.

NOTE.—Lesions on the thigh have since enlarged at an alarming rate, and I have had to resort to trenching with diathermy around the lesions. At no time has she had any fever.

Plaques on Glans Penis. Case for Diagnosis.—A. C. ROXBURGH, M.D.

Mr. S. B., aged 50.

History.—Five months ago got a red plaque on each side of the frenum. These have gradually extended both by the appearance of new plaques and by the extension of the original lesions. One Wassermann gave a doubtful positive, but a subsequent Wassermann and Kahn were both negative. In spite of this two injections of N.A.B. were given, with no improvement. Patient has never to his knowledge had either syphilis or gonorrhœa.

Present condition (January 19, 1939).—There is no evidence of psoriasis, syphilis, or lichen planus anywhere else about the body, and the lesions themselves do not suggest to me either Paget's disease or erythroplasia; for one thing their evolution has been much too rapid. There are flat plaques on the skin of the glans penis, covering the greater part of it, the largest being about 1 cm. in diameter. These are slightly infiltrated, some of them covered with adherent scale, and at the edges of the scales on some of the plaques there appears to be slight crusting as from dried serum. Removal of the scales shows a smooth dry surface. The lesions vary from time to time, but they are worse now than they have ever been. There is no irritation whatever. There is slight tumidity and moisture at the meatus.

Discussion.—Dr. INGRAM.—Do we ever see on the glans penis that type of carcinoma arising as multiple lesions in this manner?

Dr. PARKES WEBER: I think the most likely possibility is lichen planus, limited as yet to the penis. If so, the prognosis is not bad, but I consider a biopsy advisable, and the microscopical finding may contradict my suggestion.

Dr. HEGGS: I had a similar case to this second case of Dr. Roxburgh's in whom I diagnosed psoriasis. I feel in this case I would have made the same diagnosis. The patient worried me tremendously. He was almost on the verge of a nervous breakdown because of the lesions on the glans penis. I tried to calm him as best I could. He got on well with mercury and tar ointment combined with ultra-violet light treatment to the rest of the body, as a treatment of the lesion and a mental placebo.

Dr. GORDON said that he had seen a case somewhat similar to that described by Dr. Roxburgh. He had regarded the condition as possibly psoriasis, though there were no lesions elsewhere. It had cleared up with X-ray and later the patient had returned with several typical patches of psoriasis elsewhere.

Dr. ROXBURGH: In reply to Dr. Ingram I have never seen one of these precancerous growths on the penis. Those I have seen on the body have nearly always been multiple, scattered about. The condition seems to me to be progressing very fast for one of the precancerous growths, the characteristic of the latter being that they are so very slow. I shall try to persuade the patient to have a biopsy done and will report the result to the Section at some future date.

Lichen Sclerosis.—HUGH GORDON, M.C., M.R.C.P.

The patient, a woman aged 30, noticed some white patches on her chest some three years ago. These were said to come on fairly insidiously and have given rise to no irritation. At no time were they said to be raised or red. More recently further places have developed on the back.

On examination.—She has about six shiny white circular lesions on the back and a similar number on the front of the chest. In the centre of some of the lesions on the back there is well-marked keratotic plugging. The other lesions are shiny white and slightly depressed. There is no suggestion of a lilac ring nor has this ever been noticed. Mucous membranes nil.

Report on Section (Dr. W. Freudenthal): The epidermis is thinned. The rete pegs have disappeared. There is a considerable hyperkeratosis with horny plugs occupying depressions in the epidermis. The connective tissue in the upper third of the cutis is condensed and stains faintly towards the epidermis from which

it is separated in many places by a gap. In the condensed area the elastic fibres have almost disappeared except for a subepidermal garland. A small number of lymphocytes on the lower pole of the lesion is seen.

Lichen Nitidus.—HUGH GORDON, M.C., M.R.C.P.

The patient, a woman aged 24, noticed about three weeks ago an eruption appearing in front of her wrists and in the bend of the elbows, which gradually increased. Irritation was present slightly.

On examination.—On the hands punctate keratosis is present. On the front of the wrists are grouped shiny papules the same colour as the skin. In the bend of the arms there is a symmetrical plaque composed of similar papules. These are small and raised and have not the polygonal appearance typical of lichen planus. The colour of the whole eruption varies considerably. It is occasionally slightly red, but more usually flesh colour. The buccal mucous membrane shows slight punctate stippling.

Report on Section (Dr. E. Freudenthal): Under the epidermis a sharply defined granuloma is seen consisting of lymphocytes, fibroblasts, a few giant cells with nuclei arranged on the periphery, and a small amount of necrosis. There is a distinct gap between the epidermis and the granuloma. The epidermis on top of it is slightly raised, the rete pegs have disappeared: the rete is very thin and covered by a keratotic scale. On the borders of the granuloma the rete pegs are elongated and the cells are spongiotic. In another part of the section an earlier lesion is seen showing lymphocytes, fibroblasts, and a parakeratotic epidermis. On the border of epidermis and cutis, homogeneous masses are present which stain pink with H–E and yellow with van Gieson.

Dr. W. FREUDENTHAL: There is only one point I would like to add with regard to the histology. It is true that the section shows tuberculoid granuloma, but I would not like to go so far as Dr. Gordon and say that makes the diagnosis of lichen planus so unlikely. I can imagine that lichen planus gives rise to tuberculoid granuloma.

? Urticaria Pigmentosa. Case for Diagnosis.—R. T. BRAIN, M.D.

Mrs. G. H., aged 50, was first seen on January 19, 1939. She gave a history of an eruption which appeared on both arms shortly after the menopause three years ago. The eruption persisted and caused no symptoms. Occasionally a few spots have been noticed on the chest and legs. The patient had suffered from no previous skin disease. She takes no drugs.

On examination.—She was a normal healthy woman with a skin eruption almost entirely limited to the upper arms. Mainly on the posterior surfaces of these were numerous bright red macules varying in size up to 0·5 cm. Some of the lesions showed fine telangiectases. The skin surface was not scaly. A few faint macules could be seen on the forearms.

Dr. PARKES WEBER: I think this is a typical though mild example of the condition for which in 1930 I suggested the name *telangiectasia macularis eruptiva perstans* (F. P. Weber and H. Hellenschmied, *Brit. Journ. Derm. & Syph.*, 1930, **42**, 374). The patient is the characteristic stoutish middle-aged female. It is that type of patient, the rather florid middle-aged woman about the end of the menopause, or just past it, who is the most likely to get this condition, and the most typical forms of it. The present patient has, however, an incomplete form of the syndrome, in that it affects the upper extremities only. No treatment is known, but it never, as far as I know, does any vital harm and usually does not affect the face and in that way spoil the patient's beauty. As to whether or not the condition ultimately clears up, it is impossible to say. The difficulty is that these cases have not been followed up for a long time. Recently, however, there was a case in an obese girl described, which had partially cleared up, but I am not sure that one can accept that as evidence of permanent cure (F. I. Ball, *Arch. Derm. & Syph.*, 1937, **36**, 65).

Section of Psychiatry

President—H. Crichton-Miller, M.D.

[*December* 13, 1938]

Recent Trends in Psychiatry

[Abridged]

By J. E. Nicole, L.M.S.S.A., D.P.M.

Within the province of psychiatry we have our " specialists " just as we have our " general practitioners ", the specialists being those who have approached the subject from a narrow and highly technical angle and whose aims and methods apply to a part only of psychiatry. Many trends now appearing in psychological medicine owe their origin to the work of such specialists, but however much the psycho-analyst, the hypnotist, the biochemist, the histopathologist, the neurologist, and even the jurist, may have advanced their respective causes, the fact remains that the bulk of the practice of psychiatry is still in the hands of the rank and file as represented by the medical officers of our mental hospitals, who have to handle large numbers of patients under somewhat difficult conditions and who have to apply all kinds of psychiatric knowledge while steering clear of possible extremes. It is therefore from their angle that I will discuss some modern trends in psychiatry, bearing in mind that, as there are always plenty of advocates for a new treatment, it might be more profitable for me to consider their possible disadvantages.

On the clinical side we notice how of late our textbooks have rightly veered round to a description of " states " rather than of " diseases ", a change that agrees well with the fact that mental disorders lend themselves little to systematic classification and that their ætiology is so varied and multiple. Ever so often, however, the old tendency to label and pigeon-hole reappears, and in consequence more and more syndromes are described and new subdivisions of old diseases make their appearance. As a result, the junior psychiatrist is desirous of diagnosing at all costs, even where a diagnosis has little bearing upon therapy. Laboratory workers, too, are often expected to make lengthy investigations that, while affecting the diagnosis slightly, affect the treatment not at all.

Of much greater moment, however, is the progress of objective methods of investigation. A great increase of accuracy and efficiency may have resulted therefrom, but unfortunately this objective approach implies a denial of the value of any personal, individual appreciation of the patient. A student reading Cameron [1], for instance, is likely to inhibit that feeling of sympathy and desire for personal understanding which he had hitherto regarded as reasonably essential to his successful approach to a human being in distress.

Not only is clinical observation being more and more reduced to pointer readings, but the whole recording of a case is becoming increasingly mechanical and a matter of adjectives, test-scores, psychobiograms, graphs, charts, &c. Yet, because no human mind is merely the sum of so many sensations, feelings, and actions, these charts and

lists fall short of those descriptions we used to enjoy in the writings of older psychiatrists, descriptions that conjured up before us pictures of deranged and unhappy beings with such vividness and understanding that our sympathies were immediately enlisted. But now? No patient! The "human being" has disappeared and a dissected "case" has taken its place. However well we follow the voluminous instructions of Sadler [2] for case recording, or the psychobiogram of Kretschmer [3], or the graph method of Meyer, it would be hard to retranslate such a mass of data into a picture of a human mind in distress, at odds with itself, at variance with the world around, in need of our help and assistance.

Further, this growth of chart-recording has spread even to the nursing sphere, and one wonders at times how any nurse complying with the methods now being advocated in certain quarters can find time for nursing. Bryan [4], for instance, suggests that in an occupational department, reports on the patients' progress or otherwise should be made daily, as well as various charts and graphs kept, but what personal contact with the patients could a nursing official have time to achieve when she has perhaps fifty or a hundred entries to make, regardless of the fact that some of these will refer to patients that have been under her care for months. In any case it seems a good thing that we should have so far, in this country, resisted the tendency to make our nurses so technically trained that they might forget to be human beings.

Touching upon the question of research, there seems little diminution in the tendency to undertake research to order and at all costs. We are being swamped with communications, a large proportion of which have been uninspired and which have evidently never arisen from a desire for research; rather do they bear the stamp of cheap advertisement. It is not surprising, therefore, to find how much of this work is valueless, just because it has been carried out hurriedly, incompletely, on too few cases, and with a definite, preconceived bias as to what conclusions it is desired to reach. Facile generalizations and poor control also account for the downfall of much research that, if undertaken more soberly and carefully, might have proved of very great worth.

This tendency towards research, research, and still more research, may well have deleterious effects on routine clinical work. Only a few laboratories are so constructed, equipped, and staffed, as to be able to do any more than the routine investigations required by the clinical needs of the hospital, and one wonders whether some of the essential diagnostic procedures have not been sacrificed for the sake of the research turned out—especially that kind of research where the author's task is limited to the editing of material which has been patiently and loyally acquired for him by a laboratory staff, already barely adequate for the routine work required.

On the theoretical side it is interesting to see how, in spite of the schism between objective psychiatry and psychopathology already mentioned, there is a large group of workers who are so far from expecting to displace psychology by materialistic science that they recognize the existence of psychology in its own right and hold that science will never adequately explain the total personality [5]. This is surely a hopeful attitude, one that will ensure a fair share of sunshine for both the physical and mental schools. Physiology and psychology should work hand in hand, for those abstract states that form the core of psychological description and that cannot be expressed in physical terms do not float about in mid-air; they are rooted in the individual's physiology, they are modalities of an organism that is as physical as it is mental, and the extent to which they arise out of, or can be modified by, physiological states must be fully appreciated before the total organism can be adequately understood. An instance of this point of view is to be found in Misch's attempt to improve the patient's receptivity to psychotherapy by the administration of acetylcholine.

When we come to consider the question of treatment we are confronted with so many recent methods of therapy that it is impossible for us to mention each individual

one ; in any case we are really concerned more with general trends than with single treatments. We notice first of all that there has been an inclination to present certain new therapeutic devices as though they were " specifics " and constituted not only the latest and last but the only significant word on the matter. It is good to see, therefore, that a few warnings have already been given, for instance in relation to the shock treatment of schizophrenia, pointing out that the special therapeutic procedure does not cure ; rather does it pave the way for the application of other methods of treatment to which the patient had been hitherto impervious. If modern psychiatry has realized anything, it is that mental disorders have a multiple ætiology ; hence we must apply the principle of multiple treatments and not rely upon any single procedure.

Another tendency of modern practice—one which is not without its danger—is that of using certain treatments as cure-alls, to the exclusion of other treatments. As an example, let us take occupational therapy. Here we have a most valuable and important tool, the full value of which has only recently been realized, but isn't there a possibility that in our enthusiasm we might overlook the worth of exercise, of fresh air, of outdoor games (especially of unorganized games that can be spontaneously entered upon in an airing court, such as skipping, rounders, clock-golf, deck-tennis, &c.) and even of rest in bed ? Are empty beds, empty day-rooms, empty verandas, and empty airing-courts, any better than only partly filled occupational rooms ? The risk appears specially marked with recent cases, when the staff want to occupy a patient at the very earliest moment, forgetting that what may have just become possible may not yet be advisable. After states of depression and confusion the effort and sense of responsibility associated with even quite simple forms of occupation may prove a strain that might well be postponed for some time.

There is, too, the risk that some of these widely applied therapeutic measures may not receive quite the control they need ; physical training, for instance, might be applied to a physically unsuitable case. Many risks, of course, are not to be foreseen, and only become apparent as further knowledge accumulates. Already it has been said that the shock therapy by insulin may induce certain pathological changes in the basal ganglia, but as yet no definite conclusion has been reached. Prolonged colonic lavage treatment is another mode of therapy against which much has been said (e.g. by A. F. Hurst), although it was first greeted with a wave of enthusiasm, some of its risks having perhaps escaped our notice owing to our being specialized in non-physical medicine instead of in bowel diseases.

In connexion with the modern intensive search for hidden sources of infection, I sometimes wonder whether this emphasis on bodily disorders that are often remarkable for their lack of subjective symptoms may not induce in certain patients a hypochondriacal belief that more and more concealed infections might be brought to light if only sufficient search were made.

To pass to some aspects of non-institutional treatment : The rapid growth of clinics so characteristic of the last few years may create certain difficulties in staffing. The number of physicians may for a time be very inadequate and there may be a tendency to have an insufficient proportion of trained psychotherapists, thereby preventing these clinics developing beyond the stage of providing facilities for consultation, diagnosis, and administrative disposal ; they will only too slowly evolve towards the final stage of being centres for efficient and intensive treatment. At the same time, the rapidly increasing demand for social workers has strained to breaking point the various associations' resources for supplying suitable people. Success in this branch of social service can only attend those with a special aptitude for the work, and it is an unfortunate fact that a large number of women seeking training as social workers are temperamentally unsuited, however intellectually capable they may be.

I can say little concerning the theoretical and technical aspects of psychotherapy

without getting somewhat beyond my depth, but I might perhaps mention a tendency, exemplified in Schmideberg's [6], remarks on " re-assurance," to allow rather more personal influence on the part of an analyst than was formerly thought justifiable. In clinics, the treatment applied is, as a rule, of a somewhat eclectic type, so that personal influence is more likely to come into play, especially in those instances where the treatment is to be terminated within certain time limits. Is there a risk that the interpretations given, based as they often are upon the importance of the patient's childhood reactions, might in certain cases give rise to a fear of the responsibilities entailed in the bringing up of the patient's own children ?

Lay analysis still seems to be a fruitful subject for discussion and, in addition, a recent development has been an effort, in certain quarters, to bring in the question of the clergy and their role in mental therapeutics. Doctor-clergy discussion groups have been formed all over the country, and it is quite evident that many different influences and points of view have contributed to this movement, though it is not easy to assess correctly the proportion of each. Several possible aims can be discerned : (1) Doctors wish to enlist the sympathy of the clergy and to teach them just when their assistance may or may not be needed. (2) The clergy desire to recognize in time the presence of disorders requiring psychological aid and, in some instances, they wish to take an active part in the treatment. (3) There is a feeling in certain circles that it is time for religion to be re-moulded and re-worded in terms that agree better with psychological interpretations of the spiritual factor. (4) Lastly comes the " political " aim of using mental illness with its attendant spiritual problems as a means of extending the Church's sphere of influence. How all these various aims will blend, what internal dissensions may arise within these groups we cannot tell, but there seems an unfortunate likelihood that the result will be an increase of misunderstanding rather than of agreement.

In a sense, of course, we should welcome this awakening interest in matters psychological, for we must admit that our mental hygiene propaganda has been much less intensive than on the other side of the Atlantic. We might well, therefore, encourage the right kind of Press campaign ; not the kind which, as at present, limits itself almost entirely to wild demands for lunacy law reform, lurid descriptions of alleged asylum atrocities and inaccurate sensational reporting of lawsuits brought against psychiatric institutions and their staff, but a sympathetic and discriminating appeal for a better realization of the national significance of mental problems and for an alteration of the way insanity is sometimes regarded as a good excuse for either condemnation or laughter. Let us, however, avoid such journalistic exaggeration as has marred many otherwise excellent books [7] and keep to a sober, restrained approach, and from lay writers on the subject let us have more books like Winterton's [8], instead of the present-day indictments and vituperations.

When we consider psychiatry in relation to the wider problems of sociology and culture, it is difficult to discuss the present position without going deeply into ethnology. There are, however, three tendencies of some interest to us here. Firstly there is a definite recoil from the view that because psychiatry has so much to contribute to the study of sociology therefore the latter can be treated as a branch of the former [9]. Secondly, the determined effort of writers such as Unwin [10] to prove that culture varies inversely as sexual freedom, is meeting with increasingly scanty support, and the opposing view is correspondingly gaining ground, as shown, for example, in Brend's work [11]. Thirdly, there is a marked reaction against the assumption that all antisocial conduct is a pathological reaction while social standards are stable norms. Some writers would rather take the view that antisocial behaviour and collective standards may both partake of the pathological, and that they are both complementary variables, culture being as much a mirror of the human mind as the individual mind is itself a reflection of current culture. In Horney's book, for instance [12], we find a good attempt at holding the scale evenly

between the two extremes and at allowing equal importance to society and to the individual. Even the individual personal experiences and problems that make for a breakdown are themselves to be looked upon as the result of cultural influences.

But to return to some more practical considerations, this time in connexion with the law. May I first protest against the increasingly poor teaching of law. In many of our textbooks it appears as though the subject were as dry and boring to the author as it is likely to be to the reader ; the whole topic seems to be dealt with under protest and merely to substantiate a claim to completeness. Law is a necessary part of our psychiatric training, and this casual inclusion of a few legal " tit-bits " at the end of a book hardly achieves its purpose. Thus the section on law in a quite recent and excellent book on psychological medicine [13] is not only scrappy but somewhat inaccurate.

Another tendency we find in this connexion is that of giving too enthusiastic and rosy a description of modern legislation instead of a much more careful exposition of the exact limitations as well as the applications of the Mental Treatment Act. Some warning, for instance, might well be given against straining the letter of the law in order to avoid the " stigma " of certification. Indeed, this function of the Act—if function it be—seems to be invoked with quite remarkable frequency in comparison with its more strictly medical purposes. Incidentally, I have yet to appreciate the difference between the " stigma " of certification and the " no stigma " of notification, for after all every patient in a mental hospital is at least " notified " as being in receipt of mental treatment. It is perhaps a pity that the new Act almost implies that a stigma is present when for so many years the medical profession has been trying hard to get this very idea out of the popular mind.

The tendency to compromise is evident in the law itself and leads to curious positions. Thus a temporary patient is not to be retained as such for more than twenty-eight days after the return of volition. As though this return of volition were the mark that twenty-eight more days of convalescence were all the patient could possibly require before being fit to return home ! Again, a voluntary patient may leave at seventy-two hours' notice, but it seems very questionable how far he may be forcibly detained against his will, even in the absence of such notice. However, all this has so often been the subject of discussion that I shall say little more, apart from pointing out the timely introduction of slightly better safeguards for the psychiatrist, all the more opportune that the tendency to bring actions against him is so much in evidence.

Any mention of law is quite likely to bring to our minds the subject of sterilization. Dependent as this question is upon the establishment of the influence of heredity in mental disease, it is unfortunate that even now we have not yet quite freed ourselves from the error of regarding mental derangement and mental defect as unitary morbid conditions. Actually they are somewhat in the nature of symptoms, and to speak of the inheritance of mental defect at large, irrespective of whether it be associated with microcephaly, or a history of birth injury, or mongolism, or cretinism, is like discussing the inheritance of coughs, be they due to laryngitis, tuberculosis, aortic aneurysm, or emotional embarrassment. Anyway, an interesting point is that twenty years ago heredity was firmly believed in and constantly invoked, yet no question of sterilization was raised. Now, however, that we doubt much of what we once believed concerning the inevitability of heredity there is a clamour for sterilization. I leave it to the psychopathologist to deduce therefrom how little rational considerations enter into our social theories and policies.

The tendency to sacrifice some good in an attempt to eradicate the bad (if sterilization were resorted to there would be some diminution in the number of normal offspring as well as in that of abnormal ones) is a not uncommon factor in a totalitarian policy and seems to be gaining some ground at the expense of the democratic idea of putting up with the bad for the sake of keeping the good. The difficulty is, of course,

that although a democratic policy is so much a compromise between several viewpoints that it is likely to be vacillating, yet it will probably be at least as enlightened as any " single idea " method of a dictatorship. One wonders perhaps what Russia may have to teach us in this respect. I hesitate to say much about Soviet Russia, but I cannot escape the impression that under no other régime has there ever been such a real unification of outlook. There seems to be no psychiatric programme, no penal programme, no child guidance programme, no educational programme, but only one, the *State* programme, and this embodies most of what we usually associate with the aims of separate specialties, all somewhat at war with one another.

It has been said that mental derangement in Russia is definitely on the wane [14], and that important factors in this connexion are the removal of sex taboos, the economic independence of women, the freedom from child-caring of mothers who do not wish to specialize in mothering, the diminution in the likelihood of children being brought up in a hot-house atmosphere of conflicting emotions, the supply to everyone of the necessities of life, and the absence of such envy as might arise were the individual acquisition of wealth permitted.

All this, however, is somewhat far removed from our original theme, and I would return to it with the reminder that this brief and incomplete consideration of modern trends has been pursued with the idea that these tendencies, good as they are and much as they may further the aims of the specialties within which they have often arisen, have their pitfalls for the average psychiatrist who has to take as broad a view as possible and through whose hands the majority of our patients pass. It is only through awareness of his difficulties that psychiatric teaching can be properly adapted to the needs of our " general practitioner ".

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Section of Obstetrics and Gynæcology

President—ALECK W. BOURNE, F.R.C.S.

[*January* 20, 1939]

Precancerous Changes in the Cervix Uteri

By GILBERT I. STRACHAN, M.D.(Cardiff)

THE desire to know what appearances in a particular organ or structure are indicative of a tendency towards cancer formation is not new. Many observers, working on pathological changes in various organs, have sought and have described what, to them at least, have appeared precancerous changes. In the course of time, however, particular changes in certain areas have become definitely recognized as predisposing to cancer formation, and one of the most important of these is leucoplakia of the tongue; it was Berkeley and Bonney who first demonstrated a similar predilection in leucoplakia of the vulva, and in both of these conditions the precancerous qualities have been manifested clinically by the high proportion of cases which progress to epithelioma formation. In any selected organ the matter is not an easy one, and for several reasons. The proof that a condition is precancerous would lie in the supervention of carcinoma on the lesion; but in a single case this would prove nothing, it should occur in a high proportion of a large number of cases to have any significance.

Again, the actual changes in a cell from non-malignancy to malignancy have never been observed, so that a lesion at the time of observation is usually frankly malignant or non-malignant.

Further, if a particular lesion is thought likely to go on to malignancy the tendency would be to remove it, and the subsequent transition to malignancy would thus not be observed.

Finally it is not known in what the actual cancer process consists. Is it a condition affecting a single cell the derivatives of which form the actual cancerous tumour? Or are a number of cells in an area primarily and simultaneously affected by a contagious process which may extend to and influence adjacent cells towards the same condition of unrestricted and penetrative growth which is known as malignancy?

The subject, therefore, bristles with difficulties, and it follows that we must be influenced considerably in our deductions in this matter by our knowledge of general

pathological processes and principles, while any opinions expressed are bound to be, to some extent, speculative.

The cervix is a structure better adapted than most for the study of these changes as it is relatively superficial, while the trauma of labour inflicts an injury which is followed in the great majority of cases by an area of chronic irritation known as an erosion, and this erosion is generally regarded as being directly or indirectly the lesion which stimulates or vitiates the structures to carcinomatous differentiation. The following study is based on the examination of several hundred cervices removed during the last ten years, mainly for chronic inflammatory lesions, and in this sense it will be appreciated that in a few odd cases carcinoma had actually developed before removal, and was thus found accidentally. The cervix is a fibromuscular structure covered on the vaginal aspect with many layered squamous epithelium and with the canal lined by tall columnar epithelium with multiple invaginations which form compound racemose glands buried in the stroma. These two types of epithelia merge into each other normally at the external os, and it is here that carcinoma usually begins. We therefore have to inspect with care any suspicious naked-eye changes in the organ, while microscopically we have to examine the stroma and any epithelial changes. It is not proposed to describe in detail the many and often confusing appearances which may be found in a chronically eroded cervix, but certain points have to be stressed. Thus the microscopic changes have often very little relationship to the naked-eye appearance, so that in a badly eroded cervix with profuse discharge there may be very few signs of inflammation, while in a much less-marked erosion the changes, characteristic of chronic inflammation, may be definite. In many of the sections examined it would appear that the result of long-continued irritation of the cervix had been to stimulate actual adenoma formation. Eden described the appearance of a chronic erosion as pseudo-adenoma, and this description was accurate, but it is not claimed that this represents a precancerous condition as adeno-carcinoma in the cervix is relatively very rare.

Again, it is to be emphasized that ordinary naked-eye examination of the cervix usually gives no clue to the probable onset of carcinoma. So far as we have found, the lacerated, everted, badly eroded cervix is no more prone to carcinoma development than is a mere superficial erosion. What, then, is the main connecting link between the erosion so commonly encountered and the relatively scarce carcinoma ? This has been postulated by Hinselmann as a condition of leucoplakia, as in the case of the vulva. But the appearance and progress of this lesion in the cervix differ widely from the vulva and the tongue : in these regions the condition is widespread and may remain non-malignant for a considerable time. But in the cervix leucoplakia occurs in very small patches often not visible to the naked eye and requiring direct magnification by the colposcope, while it tends to be of only temporary duration and to progress rapidly to carcinoma formation ; it is for this reason that it has previously escaped notice. The colposcope is a binocular instrument fitted with direct illumination and by the insertion of appropriate eyepieces a direct magnification of from 5–20 times may be obtained. It is mounted on a heavy adjustable pedestal and can be brought instantly into focus. By its use the ordinary congested mucosa of the portio of an eroded cervix is found to have a stippled granular appearance and plaques of healing mucosa have a prominent glistening yellowish-white appearance. Hinselmann claims to find this lesion frequently, but in most clinics it is but seldom seen, and in my own department there have only been two definite examples.

Leucoplakia in the cervix consists of small, sharply defined, slightly elevated oval or circular areas on the vaginal aspect of a pale grey colour, and up to 1 cm. in diameter, but often smaller. It must not be confused with the generalized pearly pale appearance so often seen round the external os in healing ulceration in cases of procidentia. Microscopically, various appearances may be found ; thus the degree

of thickening of the epithelium and the amount of keratinization both vary within wide limits. The cells are closely packed and of irregular shape so that layer differentiation is lost, while the intercellular protoplasmic bridges are poorly marked or even absent. The cytoplasm and nuclei stain deeply and here and there an occasional mitotic figure is to be seen.

Two important histological points are that these changes end abruptly in a vertical line, and that the basement membrane is not penetrated. If this has occurred the case has already gone on to carcinoma. There is thus room for difference of opinion in the interpretation of such sections, especially when it is remembered that early carcinoma may be present before the basement membrane is penetrated. For this reason some of Hinselmann's sections have been regarded by other observers as examples, not of precancerous, but of actual, although early, cancerous changes.

In the stroma precancerous changes have been studied by Bonney, and he regarded a constant loss of the subepithelial elastic layer, lymphocytic exudation, and superficial hyaline changes as precancerous in that these factors reduce the resistance of the stroma to the penetrative down-growth of epithelial cells.

Where the elastic tissue is locally deficient local invasion in this way may be seen, and a very penetrative appearance is produced which might well go on to carcinoma.

The most suggestive lesion of this sort that we have seen is marked hyalinization in the subepithelial stroma, and this is seen only in old-standing cases. This produces a light staining area of variable depth beneath the epithelium, and it is our view that the metabolism of the epithelium is so altered by this condition that malignant changes are prone to occur. Stroma changes, therefore, may influence the later production of carcinoma in two ways, either by facilitating the down-growth of the epithelium by lack of the normal resistance, or by interfering with the normal epithelial metabolism and so predisposing to the changes of malignancy. In the epithelial structure precarcinomatous changes have to be looked for in the general architecture of cellular arrangement and in the structure of individual cells, and a large amount of work has been done on both these aspects.

It must be remembered that various degrees of epithelial proliferation may be found in the eroded cervix quite apart from carcinoma, otherwise some sections will be wrongly regarded as carcinoma and a wrong prognosis given and unnecessary radical treatment advised. One such appearance is found when regenerating squamous epithelium invades the tissues of a cervical gland and so produces an appearance at first sight typical of carcinoma. Frank and others have emphasized the necessity for the gynæcological histologist to be acquainted with such appearances before diagnosing early carcinoma. In this connexion must be mentioned cases in which, possibly through epithelial overgrowth or possibly through lack of reaction in the underlying stroma, a clump of cells becomes separated from the surface epithelium. Care has to be taken that this does not represent merely an area obliquely sectioned. Such an appearance would be considered suggestive of pre-malignancy for the reasons stated, and in certain cases of epithelioma, when the surface epithelium appears intact deep columns of carcinoma may be seen arising, in all probability from such separated clumps of cells (fig. 1).

The interpapillary down-growths are of various shapes, but usually have blunt extremities. Sometimes the columns are very sharply pointed and of a penetrative appearance. This often affects several adjacent columns and may actually resemble early carcinoma. The penetrative appearance of these columns is indicative of the probability of carcinoma supervening, and further examination of the constituent cells is indicated. In such a case several sections should be taken to exclude the possibility of the appearance being produced by oblique sectioning.

A mere increase of thickness of the surface squamous epithelium does not, in our

experience, have any significance in this way. The main precancerous changes then, are seen in the squamous epithelium ; they are not often seen in the glandular epithelium lining the canal, but occasionally here, in old-standing cases of erosion, we have seen a general tendency for the glands to revert to a simple type and to lose their racemose appearance ; this is the only observable change which might be called precancerous in this tissue.

In the examination of the individual cells local changes from the normal are to be looked for, and the more marked these are the greater would appear to be the probability of carcinoma supervening. Irregular staining of the cytoplasm giving a mottled appearance is often seen in carcinoma cells, and if present in squamous cells in chronic irritation it would suggest a tendency towards carcinoma formation. This

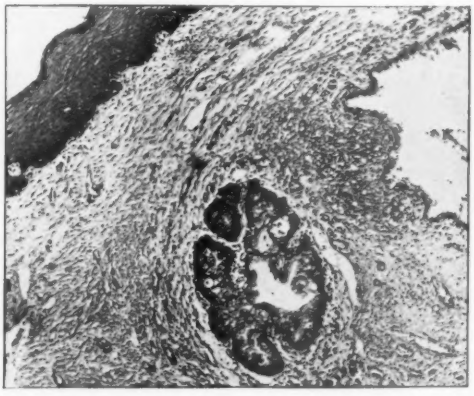


FIG. 1.—Showing a column of epithelium separated from the surface epithelium and buried deep in the stroma. In this column the changes of early carcinoma have developed but no surface carcinoma was to be found.

stippled appearance has mostly been found in cells in epithelial columns separated from the surface whose significance has been noted. In such a case several sections should be examined to exclude poor staining of one of them.

Hyperchromatism is another important point. A carcinomatous area stains more deeply than the surrounding tissue, and in this case all the cells are affected. But such an appearance may be found here and there in a non-carcinomatous chronically infected area, and especially if seen in several adjacent cells it would indicate the probability of a carcinomatous transition.

In the nucleus the most important point is the presence of mitotic figures (fig. 2) and these seen in a few cells would indicate a tendency to malignant overgrowth. The importance of the presence of mitotic figures has recently been questioned, but in our opinion it cannot be overestimated as a sign of cellular activity, and of a proneness to carcinomatous changes. If this sign be widespread it would indicate the presence of actual carcinoma.

The nucleus of a malignant cell is relatively and actually larger than in a non-malignant one, and this appearance may be seen localized to a cell or two in cases of long-standing cervical irritation. In such a case, where the appearance is marked, it

would seem reasonable to conclude that the particular cells affected were being influenced in the direction of carcinoma.

MacCarty and others in the Mayo Clinic have also found an increase in the relative size of the nucleolus in early malignancy, but we have not been able to find any evidence of this as an indication of premalignancy.

General metaplasia has also to be considered in this connexion. This is best seen in an eroded area at the junction of squamous and glandular epithelium where there is so often an infiltrated area uncovered by any epithelium. Here and there in this no-man's-land a clump of multinucleated epithelium may be seen whose origin, whether from squamous or glandular tissue is not clear, and whose progress towards malignancy would appear in some cases to be very probable. This appearance is

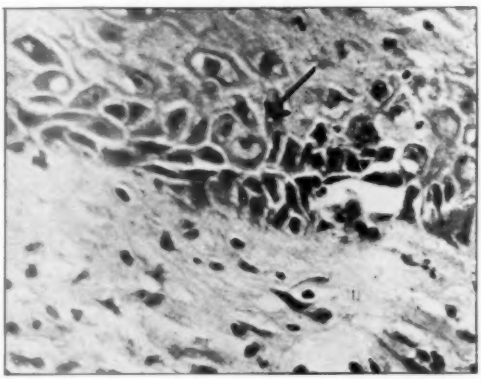


FIG. 2.—Showing mitotic figures in the surface squamous epithelium. Carcinoma was not present.

very suggestive, especially when we remember that it is in this area that carcinoma usually develops.

These, then, are the main changes that we would consider precancerous, and it was found that often more than one of them were present in a particular section, or even in a particular cell; but if they were widespread it would be fair to regard the condition, not as precancerous, but as early carcinoma. Again, in sections of actual carcinoma such precancerous changes are seldom marked, as the cancerous process usually extends rapidly and obliterates all previous changes. These changes which have been described are not numerous, and many sections have to be examined before any of them are found. The deductions I have made from the appearances observed are purely personal and frankly speculative, but it is well worth attempting to explore this area halfway between malignancy and non-malignancy.

Discussion.—Dr. W. CRAMER agreed with Professor Strachan in thinking that the clinical importance of recognizing precancerous conditions in the cervix—and indeed in all organs—cannot be overestimated. From the clinical point of view one of the most significant results of the experimental investigation of cancer has been the recognition of the fact that carcinomata arise practically always in a tissue which has been subjected to the action of a carcinogenic agent over

a considerable period of time amounting to years. As a result of this prolonged action, the tissue in which a carcinoma may subsequently arise has undergone definite pathological changes. These changes vary from organ to organ, and there may be different types of precancerous conditions for one and the same organ. In the cervix there is the further difficulty that there are two different types of epithelium. Experimentally it has been shown that a transformation of the columnar epithelium into squamous epithelium can be brought about by the action of sex hormones. In experiments carried out with Dr. E. Horning a squamous carcinoma of the body of the uterus has been produced in a spayed mouse by the prolonged action of œstrin. In the human subject such a transformation is known to occur, indicating that the cervix is subject to endocrine influences. Some of the slides demonstrated by Professor Strachan as precancerous showed such a transformation, so that this kind of metaplasia is probably a criterion of a precancerous condition for the cervix. An abnormal number of mitoses is, as Professor Strachan said, also an indication. But no criteria can be laid down *a priori* as characteristic for precancer generally. They have to be worked out for each organ empirically by patient painstaking work such as that which Professor Strachan has carried out.

Dr. L. T. Bond said that in studying both normal and pathological cervices a most noticeable thing was the instability of the epithelium, especially near the external os, but also up the canal, as shown by the ease and frequency with which the change from columnar to squamous, and vice versa, occurred ; another point was the almost invariable presence near the external os, even in apparently normal cervices, of microscopical evidence of chronic inflammation as shown by cellular infiltration.

He drew an analogy with the condition of so-called chronic mastitis, in which the cellular infiltration had at one time been considered to be of inflammatory origin but which was now attributed to endocrine imbalance ; he suggested that both so-called chronic cervicitis with glandular hyperplasia as well as cervical carcinoma might in some measure be due also to endocrine rather than inflammatory causes.

Mixed-Cell Sarcoma of the Uterus

(Abstract of Case Report)

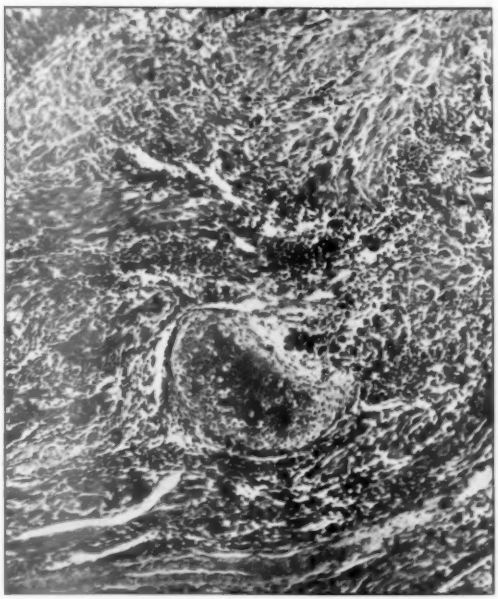
By John Stallworthy, F.R.C.S.

D. B., aged 22, nulliparous, had been married eighteen months when first seen at the Nuffield Gynæcological Department, Oxford, in October 1938. She complained of : (1) Profuse, offensive, watery vaginal discharge, occasionally blood-stained. (2) Intermittent hypogastric pain. Both symptoms had been present for one week only.

Previous history.—Operation for cervical polypi had been performed four times, with curettage on three occasions, during the last year.

On examination.—Well-developed young woman in apparently good health. The vaginal vault was filled with a cluster of cervical polypi, the cervix was softened, and the uterus was enlarged to the size of a ten-weeks' gestation.

Operation.—The polypi were removed and the uterine cavity explored with the finger. It was filled with hyperplastic-looking endometrium, 64 grm. of which were removed. Examination proved this to be infiltrated with sarcoma. As no secondary spread could be detected a total hysterectomy was performed with bilateral removal of the appendages and a wide removal of the parametric tissue. Deep X-ray therapy was commenced on the sixteenth day after operation.



Infiltration of uterine wall and area of cartilage formation.

Pathology.—The tumour is a mixed-cell sarcoma. Although the uterus is extensively infiltrated there is no involvement of the adnexæ.

Prof. STRACHAN said that the case recorded constituted an important indication of the great malignancy of certain types of mixed-cell tumour. He quoted a similar case in his own experience of a patient aged 26 years, nulliparous, with a tumour of the carcinosarcoma type of the corpus uteri. Total hysterectomy was performed, when the abdomen was found to be clean. The patient died in about a month and abdominal section then showed the entire peritoneal surfaces thickly covered with malignant material, while the liver was riddled with secondary growths. On removing the liver the undersurface of the diaphragm was found to be covered with secondary malignant growth of the same structure as the primary uterine focus.

Three Skiagrams Showing a Complication of External Version for Breech Presentation

By NORMAN WHITE, F.R.C.S.

THE patient was a primigravida, aged 27. The first film, taken during the 34th week, showed a breech presentation with the legs extended. The feet and hands were all in front of the face, and one arm had the appearance of being clasped round the legs. Version was impossible without anæsthesia as the fœtus seemed to be rather large, so an anæsthetic was administered at about the 34th week. I performed external version without much difficulty.

The second film was taken a few hours after version. It showed a vertex presentation, with the legs still extended, and the feet below the frontal region of the skull. One arm was well flexed ; the hand of the other was in front of the brow, and the forearm lay beside, not around the leg.

The third film was taken two weeks later, and showed a normal vertex presentation with both legs well flexed. The fœtus remained in this position, and a normal living child was born at term without difficulty.

Mr. J. D. Flew has reported a similar case, where labour came on fourteen hours after the version. The extension of the legs did not prevent the head engaging, and the diagnosis was made only when the cervix was three-quarters dilated, and a vaginal examination was done to ascertain the cause of delay. The child was delivered alive by internal podalic version. It had pressure marks on the anterior surfaces of both legs, and there was some sloughing of the skin, and a dropped foot on the left side, due to nerve paralysis.

The only other reference to this complication of version, which I have been able to find, is a short note by Mr. McCullagh, mentioning two cases in which obstructed labour and rupture of the uterus occurred, because the persistent extension of the legs after version of a breech presentation was not diagnosed.

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V. B. Green-Armytage, F.C.O.G., showed a colour film of Lower Segment Cæsarean Section.

Section of Neurology

President—J. G. GREENFIELD, M.D.

[*January* 19, 1939]

DISCUSSION ON THE NEUROLOGICAL COMPLICATIONS OF PREGNANCY

Dr. W. Ritchie Russell: The nervous complications of pregnancy occur infrequently, and it may be helpful in the first place to indicate briefly those diseases which may be considered in a discussion such as this.

Cerebral complications include the vascular accidents: Cerebral thrombosis, embolism, and hæmorrhage. Various forms of encephalitis which occur include chorea, Wernicke's encephalopathy, and diffuse toxic encephalitis, while the condition of multiple cerebral thrombosis forms an important complication of some cases of eclampsia. Among spinal affections myelitis is the most important. Peripheral lesions include neuritis due to pressure of the fœtal head in the pelvis or to infection of the pelvic organs, and the interesting polyneuritis of pregnancy. Muscular wasting associated with osteomalacia and polymyositis puerperalis are rare diseases. Cases of tetany should be considered, and also those in which there is some mental disturbance.

In addition to these complications an interesting study may be made of neurological diseases which are affected by pregnancy. Disseminated sclerosis, Parkinsonism, epilepsy, myasthenia gravis, and myotonia, may be considered from this aspect.

Dr. Edwin Robertson has kindly provided me with particulars of the cases admitted to the Royal Maternity Hospital, Edinburgh. During the past ten years over 23,000 patients were admitted to the hospital; among the reported neurological complications there were only 29 cases of chorea, nine of cerebral vascular accident, and four cases of polyneuritis. These figures indicate that even the better-known complications are uncommon.

I have also consulted two medical practitioners who keep detailed notes of their cases—Dr. Mackenzie of Tain and Dr. Hamilton of Loanhead. Dr. Mackenzie, who lives in a country district, has records of 1,347 maternity cases, and among these there were only two which developed neurological complications: one case of insanity following the eleventh confinement, and one case of chorea. The latter case is of interest as the patient had a severe attack of rheumatic fever a few weeks after her third confinement; a year later she became pregnant again, and at the third month developed severe chorea. Labour was induced at the sixth month, but the patient died. Dr. Mackenzie has no record of cases of injury to pelvic nerves during labour.

Dr. Hamilton practises in a part of an industrial county which has, however, no large towns. He has notes of 2,007 cases: among these there were no cases of cerebral vascular accident, encephalitis, chorea, myelitis, or polyneuritis. Six of his patients developed minor mental disturbances, but only two required institutional treatment. As regards traumatic neuritis, Dr. Hamilton reports three cases of persistent drop-foot following difficult forceps deliveries. He has no detailed record of the number of patients who complained of pain from pressure on nerves during the later weeks of pregnancy, during labour and the puerperium, but he considers that about 15% of his patients develop pains of this type.

The experience of any one neurologist or obstetrician with regard to these diseases is so small that one must turn for information to the published studies which include a collection of the recorded cases. The papers by von Hösslin (1904 and 1905) are particularly useful in this connexion. Most of the conclusions which can be derived

from a study of published cases regarding matters such as the prognosis and the desirability of terminating pregnancy, have found their way into current textbooks and, as I intend in this short communication to try to avoid entering the realm of the textbook, I shall not refer much to this aspect of the subject.

The neurologist is interested in neurological complications of pregnancy for various reasons. In the first place, accurate diagnosis may be of considerable difficulty. Secondly, the occurrence of certain complications or diseases during pregnancy may throw light on the ætiology of these diseases and, thirdly, the effect of pregnancy on established disease is of great interest for the same reason.

An important diagnostic problem, for example, is presented when the pregnant or puerperal patient becomes unconscious and the obstetrician can find no definite evidence to indicate that the patient is suffering from the effects of eclamptic toxæmia. Many of the cases in this group are found to have a vascular lesion in the brain. All the causes of coma met with in general medical practice must, however, be kept in mind, and the full investigations which such a case demands should be carried out without delay. There are certain special possibilities with regard to pregnancy and the puerperium which require emphasis.

Many recent studies of the circulation in cases of eclampsia (e.g. de Valera and Kellar, 1938) emphasize the abnormal tendency towards vascular spasm in this disease. A vascular disturbance such as this may explain many of the remarkable changes which occur in the brain and retina. A recent case illustrates the importance of vascular changes and also the clinical difficulties in diagnosis which may be encountered.

Mrs. R., aged 33, admitted to hospital in labour in the 40th week of gestation. Eight hours later a healthy baby weighing 8 lb. was born spontaneously. For two weeks before delivery the patient had complained of swelling of the limbs, and for three days there had been dimness of vision and headaches. On admission there was papillœdema and the blood-pressure was 180/115 ; the urine contained a large quantity of albumin. The day after delivery 70 oz. of urine were passed containing much less albumin, and the blood-pressure was now only 145/100. Three days after delivery the patient became unconscious and was found to have left hemiplegia. Consciousness returned and the weakness improved quickly, but three days later unconsciousness again supervened. When examined at that time the patient was stuporose, she could move all four limbs but there was an extensor plantar response on both sides—papillœdema was slight and the blood-pressure was 138/80 ; the urine contained only a small quantity of albumin. Examination of the cerebrospinal fluid showed the pressure to be 130 mm. ; there were 2 cells per c.mm. and 45 mgm. of protein per 100 c.c. Death occurred nine days after delivery and post-mortem examination showed degenerative changes in the liver and kidneys. In the brain there were multiple thrombi in the cerebral arteries with widespread infarction and partial necrosis of the brain substance. There were no hæmorrhages. There was no sign of disease of the cerebral vessels, and it seems possible that severe vascular spasm might have contributed to the condition.

Another possible cause of coma has been emphasized by Campbell and Biggart (1939) who have made a valuable study of 12 cases of Wernicke's encephalopathy. Two of these occurred in association with pregnancy, and they have reason to think that this peculiar disease of certain parts of the brain occurs more frequently in association with hyperemesis gravidarum than is generally realized.

One of their patients died at the age of 22 years. While in her sixth month of pregnancy and six weeks before death she became listless and depressed. Three weeks later vomiting commenced and became severe before death. She was semi-comatose the day before death and Cæsarean section was performed under spinal anæsthesia. The urine contained albumin and the blood-pressure was 150/115. There were no ocular palsies. In addition to the cerebral lesions there were fatty changes in the liver in this case.

The changes in Wernicke's encephalopathy are chiefly vascular and are not inflammatory. Campbell and Biggart suggest that some combination of deficiency food factors may be responsible for the disease. This condition should, therefore,

be kept in mind while considering a case of cerebral disease in pregnancy: the diagnosis may be made difficult by the occurrence of glycosuria produced by hypothalamic involvement, and acetonuria due to vomiting. These examples are sufficient to indicate the difficulty of diagnosing certain cases of coma which may occur during or following pregnancy.

Chorea gravidarum provides a problem of interest. The condition is identical clinically with rheumatic chorea, and may occur in those who have previously suffered from rheumatic chorea. Many cases have been reported in which chorea recurred with each pregnancy. These observations remind us that we really know little about rheumatic chorea: rheumatic infection alone does not account for all the facts; there must be some metabolic or deficiency factor concerned, about which we know nothing. The careful study of the patient with chorea gravidarum should throw light on the causes of Sydenham's chorea.

Deficiency diseases of many varieties occur in pregnancy and offer a fruitful field for research. Polyneuritis of pregnancy, for example, usually responds to the administration of vitamin B_1 (Strauss and McDonald, 1933), so that pregnancy can continue without interruption. Severe polyneuritis gravidarum is uncommon, but the earliest symptoms of tingling and numbness in the fingers and feet with loss of appetite are more common. The prevention of deficiency diseases in pregnancy is a matter which requires careful consideration. As far as vitamin B_1 is concerned, it is important to remember that a high carbohydrate diet, such as is sometimes advised in pregnancy, increases the vitamin B_1 requirements considerably.

Pressure of the fœtal head on pelvic nerves often causes discomfort in the lower extremities during the later months of pregnancy; this symptom may be relieved simply by the recumbent posture. In a few cases of difficult labour pressure on the pelvic nerves causes traumatic neuritis which results in various forms and degrees of motor, sensory, and reflex disturbances. These cases usually recover satisfactorily though slowly, as do cases of pressure neuritis produced in other ways. When the resulting paralysis and sensory loss only affect the lower leg it becomes highly improbable, if not impossible, that the site of neural damage can be in the pelvis. A pelvic nerve lesion which causes severe paralysis of the muscles below the knee must, for anatomical reasons, also affect muscles of the thigh and buttock. When, therefore, paralysis affects only muscles below the knee, the nerve damage is not caused in the pelvis, but is due to pressure on the common peroneal nerve and/or the tibial nerve at or near the popliteal fossa. The lesion in this case is simply a form of anæsthetic paralysis caused by pressure on the nerves during anæsthesia and is usually caused by pressure exerted to flex the thigh. I recently saw a case of this type which was probably produced by the pressure of a contraption called, I believe, an obstetric helper, which holds the thigh in a flexed position. These cases also recover gradually in the course of several months. Infection of the pelvic tissues may cause severe and painful neuritis which may also cause weakness in the legs. In such a case there is likely to be severe pain on stretching the sciatic nerve. Severe pressure neuritis caused by the fœtal head on pelvic nerves is very rare in modern obstetric practice. The more frequent recourse to Cæsarean section in cases of contracted pelvis probably lessens the occurrence of this complication.

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Dr. H. L. Sheehan: One of the main diagnostic difficulties in an obstetric hospital is provided by the patients who are admitted in convulsions or coma or with other gross cerebral symptoms. They come into hospital labelled eclampsia or toxæmia of pregnancy, and are usually treated as such unless or until they are proved to have some other condition. This communication deals chiefly with the differential diagnosis: the cerebral disturbances of the toxæmias, and the conditions which may simulate them. As my experience is limited to obstetric pathology, I shall only refer to the gross lesions that we find in the brains of such patients who die during pregnancy or the puerperium. The following table gives a rough classification of our own naked-eye findings in the last 360 brains examined at the Glasgow Maternity Hospital. In some of the other post-mortems the brains were not examined as there were no cerebral indications, so the table probably represents the lesions that would be found in about 500 or 600 obstetric post-mortems.

Lesions in brain or meninges in 360 *post mortems at Glasgow Royal Maternity Hospital.*

Meningitis	13	Miscellaneous	8
Embolism	10	Thrombosis	6
Epilepsy	5	Septic purpura	4
Glioma	4	Hæmorrhages or softening	40

The first five groups are only accidental complications of pregnancy. *Meningitis* is perhaps rather commoner than might be expected; eight of these cases were pneumococcal, three tuberculous, and the other two meningococcal. It occurs mainly in the later months of pregnancy. Usually it causes delirium and coma, sometimes there is severe vomiting, and occasionally there is a single fit followed by continuous coma, or more rarely there is a series of fits. These symptoms can cause obvious difficulties in diagnosis. *Cerebral embolism* is always due to acute endocarditis, but sometimes the heart lesion is not recognized during life. The left middle cerebral is usually affected. It may occur during pregnancy or, less often, in the puerperium. The usual symptoms are sudden coma and hemiplegia, without fits. We have had some peculiar cases in patients who were apparently quite well, and had an anæsthetic for operative delivery. Instead of coming out of the anæsthetic, they remained in coma without any obvious reason clinically, and died in two or three days. The cause of the coma was found to be cerebral embolism, at post-mortem. (Of course, similar post-operative coma can be due to various other causes.) *Epilepsy* can sometimes go on to fatal status epilepticus towards the end of pregnancy. This may give a very good imitation of eclampsia, and probably accounts for some of the cases reported in the literature, where a patient has hundreds of so-called eclamptic fits. The main interest of these cases is that they provide pathological material where there have been convulsions and coma during pregnancy, without eclampsia. In such cases there are never any eclamptic lesions in the brain or elsewhere in the body. *Gliomata* form a related subject. Two of our cases were very small cortical gliomata which gave a long history of epilepsy culminating in fatal status epilepticus towards the end of pregnancy, with no other indication of their presence. The other two were gliomata in the substance of the brain with increasing hemiparesis, and finally death in coma. The *miscellaneous group* includes quite incidental conditions unrelated to pregnancy, such as hydrocephalus, tabes dorsalis, disseminated sclerosis, and so on.

The remaining conditions are more directly related to pregnancy. *Puerperal thrombosis* covers those cases where thrombosis develops in certain of the meningeal veins entering the superior longitudinal sinus. This produces an area of softening in part of the cortex, usually about a couple of inches in diameter. The history is nearly always the same. The patient has a normal delivery, and a normal puerperium without any obvious clinical sepsis. Then, three to ten days after the delivery, there is a sudden onset of fits and coma. The coma is rarely prolonged or deep, but

the fits may continue for some days. The softening may involve the motor area and cause hemiplegia, but many of the cases have only the frontal or occipital lobe affected, and have no obvious localizing symptoms. This condition accounts for nearly all the cases that are diagnosed as " late eclampsia ", where fits begin after the first day of the puerperium. The group labelled *septic purpura* is of little interest here ; it includes petechial hæmorrhages in the white matter or pia-arachnoid related to sepsis.

The last group is the most interesting one : it deals with the toxæmias of pregnancy. Taking first the patients who die of *eclampsia* or of *coma supervening in pre-eclampsia :* many of the cases have no gross cerebral lesions ; there may be a report of œdema or congestion of the brain at autopsy, but these findings have to be regarded with the greatest suspicion as they are so frequently only artefacts. Flattening of the convolutions may also be present ; its significance is rather doubtful. The most striking point, however, is the frequency of cerebral hæmorrhages or softenings or meningeal hæmorrhages in these cases. Such lesions were recognized with the naked-eye at post-mortem in over a third of our cases : in 24 out of 67 true eclamptics, and in 14 out of 31 pre-eclamptics who developed coma with no fits or with only a single initial convulsion. In addition many of the others had hæmorrhages which could only be found on microscopic examination. These cerebral hæmorrhages are quite distinct from those seen in arteriosclerosis. They are of three main types : (1) Pontine hæmorrhages ; of various sizes up to quite large ones that rupture into the 4th ventricle. (2) Lesions of the basal ganglia ; diffuse early softening, or capillary hæmorrhages which sometimes pick out the caudate nucleus or the back of the thalamus, or sometimes large hæmorrhages. (3) Cortical lesions ; either capillary hæmorrhages or minute softenings, or petechial hæmorrhages in the overlying pia-arachnoid, and very variable in extent and distribution (fig. 1).

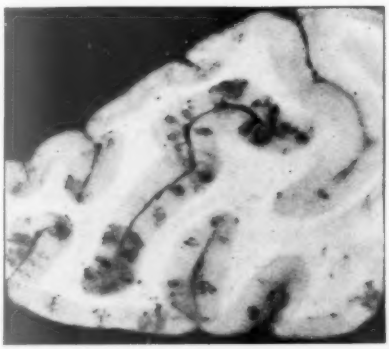

FIG. 1.—Capillary hæmorrhages in occipital cortex, in eclampsia.

Less commonly there may be subcortical hæmorrhages 1–3 cm. in diameter, or rarely hæmorrhages into the region of the internal capsule. Microscopically there are thrombi in some of the capillaries or supra-capillaries ; these give a fibrin staining reaction, but they are often peculiarly colloid in appearance. Sometimes there is a fibrin or fat deposition in the walls of these smaller vessels, and around these thrombosed or damaged vessels there is often some softening or hæmorrhage. These lesions cannot be related satisfactorily to the hypertension which is often mild, nor to the asphyxia of the convulsions, as they do not occur in epilepsy and may occur in pre-eclampsia. Old-standing vascular disease or cerebral aneurysms are only rare

factors. From the microscopic appearances it seems very possible that the lesions are secondary to some gross vasomotor disturbance in the cerebral vessels. Such a disturbance is probably present in all eclamptics and would account for the convulsions and coma. Probably in most cases of eclampsia the local circulatory disturbance is insufficient to produce any hæmorrhages or softenings. If they do occur, the eclampsia *itself* is presumably nearly always fatal, irrespective of whether the cerebral lesions are of a large fatal kind or are only small. The evidence for this is that recovery from eclampsia is usually perfect from a neurological point of view. Residual hemipareses are almost unknown, and subsequent epilepsy due to the cortical damage is a similar rarity. There are great difficulties in the clinical diagnosis of cerebral hæmorrhage in a patient who is in eclamptic coma. Attacks of severe cyanosis suggest a large pontine hæmorrhage, and an unvarying hemiplegia suggests a large hæmorrhage in the basal ganglia.

One point of interest in relation to eclampsia is the condition of the brain in *cortical necrosis* of the kidneys. Some of these patients die long before they ought to, if the renal lesions alone were responsible. Sometimes they get minor fits a few days after delivery, and may die in coma at four to eight days after delivery. At post-mortem, these cases sometimes have multiple small softenings in the brain. It is not clear whether these are due to an acute degeneration in the cerebral vessels, comparable to that which occurs in the kidneys, or whether the lesions are related to those of eclampsia.

In *hyperemesis*, the starvation and metabolic disturbances are serious factors, but, in themselves, they are scarcely ever fatal. Death occurs usually in one of two ways : about a third of the deaths are due to post-operative shock or coma, following the induction of abortion, and are of little neurological interest ; the other two-thirds of the deaths result from a special kind of cerebral syndrome rather similar to a Korsakoff. Once this cerebral syndrome is well established it seems to be nearly always fatal, usually in about five to ten days, though the newer lines of treatment may save the patient. The general clinical story is as follows : After several weeks of severe hyperemesis, the patient stops vomiting rather suddenly but the pulse-rate remains high or increases. Then she becomes apathetic or drowsy, and is found to have nystagmus. She may become very loquacious, or develop tenderness of the legs. More marked eye symptoms may develop—squint, retinal hæmorrhages, blindness, and so on. Sometimes medullary nerve symptoms follow—nasal regurgitation of fluids, or hoarseness of the voice. Then, after a short phase of mental confusion, the patient goes comatose and dies. This clinical condition is so clearly cerebral that the cases are sometimes diagnosed as encephalitis.

There has not been any clear line as to the pathology of this cerebral syndrome until the recent and very excellent work of Campbell and Biggart (1939). They worked on a much wider and rather different field—the cerebral changes in ordinary hospital patients, male or female, who died of coma, chiefly following gastro-intestinal diseases and particularly carcinoma of the stomach. In these patients they found the lesions of Wernicke's encephalopathy, which had previously been recognized as the pathological basis of the Korsakoff syndrome. What is of particular importance here is that, of their 12 cases, two were pregnant women who died of coma at about five months. Both these women had had a certain amount of vomiting, though only one was a typical hyperemesis. The naked-eye changes of Wernicke's encephalopathy are pin-point hæmorrhages in certain parts of the brain-stem, with a perfectly symmetrical arrangement. These are related to microscopic changes in the capillaries. The lesions can best be illustrated by a case we examined recently. She was a true hyperemesis from the 4th to the 13th week. Then she developed this cerebral syndrome in a very complete form, and died in five days. She had every one of the signs and symptoms described above. At post-mortem she had petechial hæmorrhages in the lateral walls of the 3rd ventricle and in the corpora mammillaria

(fig. 2), in the inferior corpora quadrigemina, and in the medulla just below the floor of the 4th ventricle (fig. 3). Microscopically there was in these regions an apparent excess of capillaries with hyperplasia of their endothelial and adventitial cells. There was some microglial proliferation. Most of the nerve-cells appeared normal except in the inner half of both olivary nuclei, where they were all completely necrosed.

The question that arises is whether this Wernicke lesion is at the root of all these peculiar cerebral deaths in hyperemesis ? From the distribution of the lesions, they could obviously account perfectly for every one of the symptoms. The difficulty is

FIG. 2.—Capillary hæmorrhages in inner thalamus and corpora mammillaria, in hyperemesis.

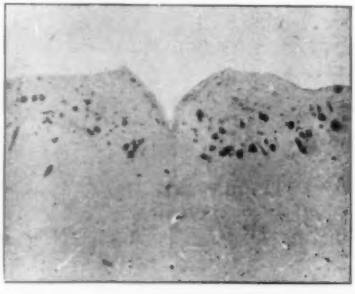

FIG. 3.—Capillary hæmorrhages in floor of 4th ventricle in hyperemesis. (× 5)

that most people who have examined the brain in hyperemesis have found no lesions at all. Case 3 of Berkwitz and Lufkin (1932) is quite a clear Wernicke lesion ; one of their other cases is possibly a healing stage. Other less certain cases are recorded by Siemerling (1917) and Schjøtt-Rivers (1938). It seems very possible that some other pathologists may have overlooked the lesions, not knowing the places to search. I have examined two hyperemesis brains recently and have found the lesions in both of them. Further studies are, however, required before it will be known whether the lesions are constant or not in this cerebral syndrome following hyperemesis. The

lesions are probably only a result of the hyperemesis, and Campbell and Biggart regard them as related to a local anæmia, possibly due to vitamin B_1 deficiency.

There has been very little pathological study as to two possibilities of *hypothalamic lesions* related to pregnancy. (1) Some women develop marked obesity after a delivery. In a few cases this is associated with marked polyuria and a great water-thirst. I have not had the opportunity of examining the hypothalamus in such a case, but there ought to be some pathological explanation. (2) Recent necrosis of the anterior pituitary is of course a common finding in the puerperium after collapse at delivery, and some of these patients die in coma. In admittedly rather cursory examination of the brains in these cases, I have not noticed any obvious lesions in the hypothalamus. In the healed stage of the lesion, when Simmonds's disease has developed, there may be mental symptoms. The brain is usually reported as normal, but Gallavan and Steegman (1937) found gross atrophy of the supra-optic nucleus, and Bini (1937) found a similar atrophy of both the supra-optic and supra-chiasmatic nuclei. I have only made a careful examination of one case of the healed pituitary lesion, and in this the symptoms had not been very marked. There were no abnormalities in the hypothalamic nuclei in this particular case, but the subject certainly merits further pathological study.

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Dr. Redvers Ironside : *Neuritis complicating pregnancy.*—Stimulated by the findings in beri-beri by Peters and his associates (1938, *et al.*), clinicians, physiologists, and pathologists have turned their attention to various forms of nutritional polyneuritis hoping to demonstrate a similar vitamin B_1 deficiency.

Gestational polyneuritis has been likened to chronic beri-beri by enthusiastic workers in this unexplored field. This is not unreasonable, for the pathological findings in gestational polyneuritis are similar to those of experimental and acquired beri-beri. Moreover, gestational polyneuritis may occur in women having insufficient or improper food, or who are starved from hyperemesis : and the pregnant mother by reason of the presence of the growing fœtus and her raised basal metabolic rate (20%) has a relatively high vitamin B_1 requirement.

While the two diseases bear a pathological resemblance to each other and to other forms of polyneuritis, they are clinically clearly dissimilar. The massive œdemas of wet beri-beri are never met with in gestational polyneuritis, nor does one see the acute cardiac failure with epigastric pain, extreme restlessness and dyspnœa in which death is dramatically averted by injection of vitamin B_1 (Brunel Hawes, 1938). If the infant survives the maternal polyneuritis it presents none of the disquieting symptoms of infantile beri-beri.

It is admitted that in the neuritic forms of beri-beri the nervous condition is cured quickly by vitamin B_1 only in some cases, in others the symptoms take months to disappear.

If the polyneuritis is due to vitamin B_1 deficiency, as so many have asserted, it should be arrested by adequate substitution therapy and appropriate feeding. But in the gestational cases following hyperemesis described by Luikart (1933) and Bingham (1936) the polyneuritis progressed to a fatal issue in spite of vitamin B_1 administration and suitable feeding. Inadequate dosage or other factors have been blamed for these failures.

Peters (1938) has shown that vitamin B_1 deficiency causes dysfunction of certain

cells in the brain, and secondary changes in carbohydrate metabolism arise therefrom. The effects of a deficiency are therefore complex and indirect (Walshe, 1920).

It is helpful to separate and describe first the gestational polyneuritis which occurs in *the absence of demonstrable toxæmia* as it is commoner and milder than the well-defined and dangerous type which follows hyperemesis gravidarum.

(1) *A cyetic polyneuritis occurs in the absence of any demonstrable toxæmia.*—It begins at the fifth or sixth months of pregnancy, and at the onset the neuritis may be confined to an individual nerve (e.g. ulnar, external cutaneous nerve of the thigh). The condition later becomes generalized, and may be accompanied by Korsakoff's psychosis, but it is always relatively mild and clears up a variable time after parturition. In the pregnancy cases alcoholism, abortifacients (e.g. apiol) and other toxic, metabolic, and infective causes have to be ruled out. Puerperal cases occur in the absence of infection or demonstrable toxæmia. Nephrotoxic signs are absent, and if œdema of the face or limbs is present it is always slight.

All obstetricians have seen a few of these cases, and there are many in the literature. I myself have seen two recovering cases after parturition, both with complete absence of hydrochloric acid from the gastric juice ; but this gastric anacidity is not a constant finding. Abnormal anæmia and signs of tetany were absent in my cases.

Stähler (1937) reported 15 cases in an examination of 4,000 poorly nourished pregnant women in Frankfurt, the wives of unemployed on the dole. This incidence is higher than in this country. It is noteworthy that both my patients were well nourished and there was no history of anorexia.

(2) *Polyneuritis following hyperemesis gravidarum.*—This is a rare and dangerous disease, with a very characteristic clinical picture deserving better notice in the textbooks. Cases were first collected by Turney (1896), later by von Hösslin (1905), and in 1932 Berkwitz and Lufkin collected 36 cases of this type from the literature of fifty years and added four personal and fatal cases.

Since their paper, cases have appeared with greater frequency in the journals, and I have been able to collect and tabulate a further 31 cases published since 1932. The records of the Simpson Memorial Hospital (Edinburgh), where the admissions total 2,500 annually, reveal one case each year for 1933–35. Hyperemesis is said to be commoner in Scotland than in England. The frequency of the syndrome may be put at one in many hundreds of thousands of pregnancies, and many experienced obstetricians have never seen a case. The concomitant Korsakoff's psychosis may send some patients direct from the antenatal clinic to the mental hospital.

Pathology.—The changes found are similar to those of any toxic polyneuritis. Myelin degeneration is present in the peripheral nerves in most cases. The spinal cord shows chromatolytic changes in the ventral horn cells. In a few cases with Korsakoff's psychosis the brain has been studied by modern staining methods (Wilson and Garvey, 1932), Berkwitz and Lufkin (1932). The cortical cells are not recorded as showing the lipochrome deposits described by Carmichael and Stern (1931) in alcoholic cases of Korsakoff's psychosis.

The brain and cord may show changes of a different order. Petechial hæmorrhages are rather commonly present, particularly in the hypothalamic region, the floor of the 4th ventricle, and the medulla (Berkwitz and Lufkin, 1932, de Carle, 1936).

Clinical.—Vomiting commences in the first or second month of pregnancy, and is severe and incessant. Hardly anything is retained, and the patient becomes dehydrated and emaciated. The loss of weight is considerable, figures range between 20 and 80 lb., and jaundice is common. Just before the onset of polyneuritis the vomiting may abate ; the latent period between the cessation of the vomiting and the onset of the polyneuritis may be one to three weeks.

The polyneuritis comes on from twelve to twenty-four weeks after conception, but the onset may be delayed until after parturition. In acute cases the helplessness of the patient may be erroneously ascribed to extreme prostration (Forman, 1937).

Author Year	Age Gravida	Hyper-emesis	Motor symptoms: Onset	Type	Distribution	Degree	Sensory symptoms	Incontinence
Hoffman, 1932 ..	32 yrs. ii	+++ 3rd mo.	4th mo.	l.m.n.	Upper and lower limbs and bulb.	Severe	Peripheral analgesia	
Wilson & Garvey, (1) 1933	19 yrs. i	+++ 4th mo.	5th mo.	l.m.n.	Lower and upper limbs	Severe	Numbness of hands and forearms	+
,, (2)	21 yrs. i	+++ 3rd mo.	6th mo.	l.m.n.	Lower and upper limbs	Severe	Ataxic	+
,, (3)	30 yrs.	+++	4th mo.	l.m.n.	Upper and lower limbs	Moderate	Hyperæsthesia of hands and feet	
Lubin, 1933 ..	i	+++ 2½ mo.	5th mo.	l.m.n.	Upper and lower limbs and ocular muscles	Moderate	Muscular tenderness. P.S. absent in fingers and toes	
Luikart, 1933 ..	31 yrs. iii	+++ 2nd mo.	3rd mo.	l.m.n.	Upper and lower limbs and dysarthria	Severe	Muscles tender. Numbness of hands and feet	+
Prior, 1933 ..	vi	+++	4th mo.	l.m.n.	Upper and lower limbs	Severe	Paræsthesiæ. P.S. and V.S. absent	
Strauss & McDonald 1933 (1)	32 yrs. i	+++ 4th mo.	6½ mo.	l.m.n.	Upper and lower limbs	Moderate	Muscles tender	
,, (2)	30 yrs.	+++ 2nd mo.	4th mo.	l.m.n.	Upper and lower limbs	Moderate	Paræsthesiæ	
,, (3)	40 yrs. iii	+++ 2nd mo.	4th mo.	l.m.n.	Upper and lower limbs	Mild		
Vandel, 1933 (1)	26 yrs. i	+++ 3rd mo.	4th mo.	l.m.n.	Chiefly lower limbs	Mild	Paræsthesiæ	
,, (2)	40 yrs. vii	+++	6th mo.	l.m.n.	Upper and lower limbs	Moderate	Paræsthesiæ	
Fouts, Gustafson & Zerfas, 1934	29 yrs. i	+++ 2nd mo.	4th mo.	l.m.n.	Chiefly lower limbs esp. left	Moderate	Cramps and numbness in hands and feet	
Gerstle and Lucia, 1934	22 yrs. i	+++ 3rd mo.	3½ mo.	l.m.n.	Upper and lower limbs and bulb.	Severe	Paræsthesiæ. V.S. and P.S. absent	+
Gillespie, 1934 ..	27 yrs. ii	+++ 2nd mo.	5th mo.	l.m.n.	Upper and lower limbs and respiration	Ascending Severe	Numbness and pains in lower limbs	
Schaupp, 1934 ..	33 yrs. ii	+++ 1st mo.	4th mo.	l.m.n.	Upper and lower limbs and ocular muscles	Severe		+
Stroh, 1934 ..	27 yrs. iii	++ 2nd mo.	3rd mo.	l.m.n.	Upper and lower limbs and bulb.	Moderate	Pains and hyperæsthesia of muscles	
Chavany et Thiébaut, 1935	32 yrs. ii	+++ 1st mo.	2nd mo.	l.m.n.	Upper and lower limbs	Severe	Pains and hyperæsthesia P.S. absent	+
Cook, 1935 ..	28 yrs.	++	6th mo.	l.m.n.	Upper and lower limbs	Moderate	Tendon muscles and " pins and needles "	
Värynen, 1935 (1)	32 yrs. i	+++ 1st mo.	3rd mo.	l.m.n.	Upper and lower limbs	Moderate	Paræsthesiæ in fingers	+
,, (2)	31 yrs. ii	+++ 2nd mo.	3rd mo.	l.m.n.	Upper and lower limbs	Moderate	Pains in limbs	+
,, (3)	29 yrs. ii	+++ 2nd mo.	6th mo.	l.m.n.	Lower and upper limbs and ocular musc.	Mild	Pains in limbs. Deep musc. tenderness	
,, (4)	27 yrs. ii	+++ 2nd mo.	3rd mo.	l.m.n.	Lower and upper limbs	Mild	Tenderness of muscles	+
,, (5)	27 yrs. iii	++ 1st mo.	4th mo.	l.m.n.	Lower limbs chiefly	Moderate	Tenderness of muscles	
Bingham, 1936 (1)	37 yrs. v	++ 2nd mo.	3rd mo.	l.m.n.	Upper and lower limbs	Mild	Ataxic with loss of P.S.	
,, (3)	34 yrs. i	+++	4th mo.	l.m.n.	Upper and lower limbs	Severe		
,, (4)	24 yrs.	+++ 1st mo.	2nd mo.	l.m.n.	Upper and lower limbs, chiefly legs	Mild	Peripheral anæsthesia	
de Carle, 1936 ..	33 yrs. ii	+++ 2½ mo.	3rd mo.	l.m.n.	Upper and lower limbs	Mild	Tenderness of muscles	
Forman, 1937 ..	17 yrs. i	+++ 1st mo.	2nd mo.	l.m.n.	Upper and lower limbs	Severe	Analgesia and anæsthesia V.S. and P.S. absent	
Stähler, 1937 ..	22 yrs. i	+++ 2nd mo.	5th mo.	l.m.n.	Upper and lower limbs	Mild	Cramps and pains in hands	
Ungley, 1938 ..	22 yrs. ii	+++ 2nd mo.	4½ mo.	l.m.n.	Upper and lower limbs	Severe		

NOTE.—l.m.n. = lower motor neurone. V.S. = vibration sense. P.S. = position sense.

Cases Reported Since 1932.

Mental symptoms	Hgic. retinitis	N. deafness Nystagmus	Gastric analysis	Additional data	Subsequent history	Termination
Korsakoff's psychosis	+	Nystagmus		Hypochromic anæmia B.P. 116/74	Fœtus died *in utero*	*Death* on 12th day of paralysis
4th mo. Korsakoff and hallucin.		Nystagmus		Jaundice. Tr. alb. *No* loss of wt. B.P. 120/88	Therapeutic abortion 6th mo.	*Death* from respiratory failure on 11th day
5th mo. Drowsy + Korsakoff		N. deafness (bilateral) Nystagmus		Lost 35 lb. in wt. Sec. anæmia ++ B.P. 90/60	Therapeutic abortion 6th mo. Dead ovum (3½ mo.)	*Death* on 13th day
4th mo. Korsakoff		Nystagmus		Loss of wt. Jaundice	Therapeutic abortion 3rd mo.	*Death* 5 mo. later. Jaundice
0		Nystagmus		Jaundice. Pulse = 120/min.	Therapeutic abortion 5½ mo.	*Death* 3½ mo. later
4th mo. Korsakoff	+	Nystagmus		Lost 50 lb. in wt. B.P. 130/75 P. 90/min.	Vit. therapy of no avail	*Death* 5th mo. after conception
Korsakoff Delusions						Symptoms persisted
0			Achlorhydria	Macrocytic and poikilocytic anæmia	Therapeutic section 6th mo. Dead fœtus	*Recovered* after months
Korsakoff					Spont. abort. maceration fœtus 5th mo.	*Recovered* after months
Psychotic				Macrocytic and hypochromic anæmia	Delivery at term Healthy child	*Recovered* after months
0			Achlorhydria	Emaciation marked. Hypochromic anæmia B.P. 110/50. P. 110/min.	Delivery at term High vit. diet	*Recovered*
0			Achlorhydria	Hypochromic anæmia Vincent's infection mouth	Delivery at term High vit. diet	*Recovery* during pregnancy
Korsakoff				Lost 27 lb. in wt. B.P. 130/90. P. 130/min.	Delivery at term	*Partial recovery* dur. pregnancy
Confused	+ Temporary blindness	Nystagmus	Anacidity	Lost 30 lb. in wt. Hypochromic anæmia	Spontaneous abortion at 3½ mo.	*Recovery*
0				Lost 35 lb. in wt.	Therapeutic abortion 4th mo.	*Recovered*
Stupor	+	Nystagmus			Therapeutic abortion 4th mo.	*Death* 3 days later
Korsakoff's psychosis		Nystagmus		Lost 40 lb. in wt. Icteric	Therapeutic abortion 4th mo.	*Recovered*
Somnolence + Korsakoff		Nerve deafness			Therapeutic abortion 3rd mo.	*Death* 3 mo. later
Korsakoff				Recovered on vit. B_1	Delivery at term	*Recovery* during pregnancy
Confusion		Nystagmus		Jaundice P. 110/min.	Therapeutic abortion 3rd mo.	*Death* 5 days later
Disorientated				Jaundice Slight œdema	Therapeutic abortion 3rd mo.	*Death* 20 days later
0				Porphyrinuria	Therapeutic abortion 5th mo.	*Death* 12 days later
4th mo. Korsakoff's psychosis Disorientated		Nystagmus		Jaundice	Spontaneous abortion 4th mo. Spontaneous abortion 4th mo.	*Recovery* after months *Recovery*, partial
"Nervous"				Lost weight	Therapeutic abortion 4th mo.	*Recovery*
4th mo. Confusional				Exophthalmos	Therapeutic abortion 5th mo. Vit. B given	*Death* 7 days later
2nd mo. Lethargic Confusional				Jaundice	Therapeutic abortion 2nd mo.	*Recovery* after months
	+			B.P. 105/70	Therapeutic abortion 4th mo.	*Death* 3 days later
Korsakoff's psychosis				Hypochromic anæmia Blood W.R. positive	Therapeutic abortion 2nd mo.	*Recovery* after months
				Slight œdema B.P. = 120/85	Delivery at term	*Recovery*
			Anacidity		Spontaneous abortion 4th mo.	*Recovery*

Note.—See Bibliography to above cases, page 41.

Peripheral paræsthesiæ, cramps, and extreme muscular tenderness, are succeeded by a flaccid, jerkless paralysis of the limbs sometimes ascending, sometimes involving the ocular muscles or the face. In most cases the highest terminals of the nervous system become involved with the appearance of Korsakoff's psychosis. Auditory hallucinations, delirium, and drowsiness, are less common. Tachycardia is almost uniformly present, and bulbar signs or respiratory paralysis occur in the gravest cases.

Two symptoms deserve special mention :—

(1) Nerve deafness and nystagmus : Nystagmus is recorded with such frequency that I believe I am right in describing it as a special characteristic of this polyneuritis. Unilateral or bilateral nerve deafness may accompany the nystagmus (Dawson, 1937).

(2) Hæmorrhagic retinitis : Slight degrees of optic or retrobulbar neuritis with rapid loss of vision may be present, accompanied by retinal or subhyaloid hæmorrhages (Schiotz, 1921, Stander, 1932, Tillman, 1934).

Both these symptoms are perhaps commoner in severe hyperemesis gravidarum uncomplicated by polyneuritis. In the light of necropsy findings they are probably the expression of more profound changes in the brain. Unlike the other symptoms, they clear up speedily after the uterus empties.

Gastric analysis.—Gastric anacidity or achlorhydria is reported rather frequently, but an insufficient number of records are at present available to ascertain whether this is an important clinical feature.

Achlorhydria is not a usual finding in hyperemesis ; Strauss and Castle (1932) examined the stomach contents of 24 normal women throughout pregnancy, and found low hydrochloric acid and pepsin activity in most with return to normal after parturition. 12% of these normal cases had total and persistent achlorhydria with no return of free hydrochloric acid after delivery.

The urine, blood-pressure, cerebrospinal fluid, and spinal fluid pressure, are normal.

Laboratory estimations of vitamin B_1.—Observations are exceedingly few. The vitamin may be estimated in the blood, in the urine, or a tolerance test may be performed.

Different observers use different techniques, and all investigations are hampered because biological assay and chemical methods so far employed are not sensitive enough to measure the minute quantities present in the blood (Rowlands and Wilkinson, 1938). Peters (1938) gives the average normal reading as 0·008 mgm./100 c.c. blood, using the azo test (Kinnersley and Peters, 1930), or Jansen's thiochrome method (Kuhn, Ritsert, 1938).

H. M. Sinclair (1939), using Schopfer's yeast technique (1935–37), found low values but no symptoms in pregnant women from Glossop on poor diets. On the other hand, in six cases of gestational polyneuritis he found a low value in one case only. All the others were normal.

Ungley (1938), using Schopfer's yeast technique, found 0·007 mgm./100 c.c. blood in one hyperemesis case, a reading which is not particularly low. He comments in this case on the low urinary excretion of vitamin B_1 and lack of response to a test dose. Stähler (1938) too, in his case, using a thiochrome technique after 10 mgm. aneurin given intramuscularly on four successive days, found poorer excretion than in normal pregnancies.

He does not say, however, if his cases were on a constant diet. His findings were :—

	Percentage total excretion of the 40 mgm.
Non-pregnant women	46%
Healthy pregnancies	30%
Gestational polyneuritis	11%

Avitaminosis Theory

The evidence for vitamin B_1 defect is at present slender. Therapeutic successes are of little worth as the disease when mild tends to spontaneous cure, and in the cases published liver extract, cod-liver oil, orange juice, and adequate diets, were given as well as vitamin B_1. It is certain thath in severe cases deatfrom advancing paralysis has not been arrested by vitamin therapy.

Clinically the pregnancy cannot be the cause of the syndrome because (1) the symptoms may progress after the uterus empties, and (2) partial recovery may take place during pregnancy (Fouts, Gustafson and Zerfas, 1934). It is possible, of course, that pregnancy toxæmia induces a disorder of metabolism which persists after parturition, but this is unlikely as the polyneuritis may recur later in life independently of pregnancy after intervals of complete freedom from symptoms (Päkozdy, 1929).

Prognosis and Management

In Berkwitz and Lufkin's 36 cases the mortality was 25%. In my series of 31 cases, probably recognized earlier, the mortality was 43%.

The paralysis may recur in subsequent pregnancies or may be permanent (Schatz, 1933). The psychosis may persist and progress to dementia. In most of the non-fatal cases the psychosis recovers and later the paralysis disappears more or less completely over a period of two months to two years. I am not convinced that termination of the pregnancy arrests the polyneuritis, although it may be necessary on obstetric grounds to control the hyperemesis.

If vitamin B_1 is administered the adequate daily dose is 50 mgm. aneurin intravenously in severe cases combined with suitable feeding. Overdosage is said to be harmless in true polyneuritic cases, but Stähler has reported that in the last month of pregnancy in normal women large doses may cause uterine contractions and fœtal anoxæmia.

(3) *Polyneuritis in recurrent pregnancies.*—Cases have been reported by Ormerod, 1895 (primigravida, aged 21 years, onset at fifth month of pregnancy with recurrences in four successive pregnancies), and Batten, 1912 (recurrences after two successive parturitions). Hyperemesis was not present. Maisel and Woltman have more recently reported a similar case (1934). In Ungley's (1933) remarkable cases polyneuritis of irregular distribution affected a mother and two daughters at different times over a period of twenty years, the polyneuritis showing a marked tendency to recur during pregnancy and parturition. In Päkozdy's case (1929) the polyneuritis recurred independently of pregnancy on three subsequent occasions. No thickening of peripheral nerves was demonstrable in any of these cases.

(4) *Parturitional paralysis.*—This name is given to rare cases of foot-drop occurring after parturition. The condition is commonly said to be unilateral and to affect the extensors of the toes, tibialis anticus, and peronei, i.e. the muscles supplied by the common peroneal nerve. It is usually ascribed to *pressure* of the fœtal head on the lumbosacral roots (L 4, 5) or of the strap hitching up the knee on the obstetric operation table on the peroneal nerve as it crosses the head of the fibula, to *traction* on or *trauma* of the lumbosacral plexus on forceps delivery, or to pelvic *infection*.

No pathological data are available. Do all these causes explain the clinical facts ?

(1) The condition is exceedingly rare ; if pressure were the sole cause it should be found more frequently, and in pressure cases one would expect the ureter and great vessels to be damaged as well as the nerve-roots.

(2) In certain unilateral cases the presentation was L.O.P. (Tillman, 1935) or L.O.A. (Lambrinudi, 1925), yet the paralysis was in the right foot.

(3) In some cases (Lamy, 1896, Tillman, 1935), the paralysis was bilateral and affected the thigh muscles as well as the peroneal group.

(4) A latent period of two to nine days may elapse between parturition and the onset of the paralysis (Hinds Howell, 1908), sepsis being excluded.

(5) Tinglings may be present in the fingers during pregnancy (Morgan and Thomson, 1935) or bilateral sciatic pains occur before the head engages (Rodway, 1935).

I submit that the common factor behind most of these cases is an unsuspected gestational polyneuritis and that this explanation alone will account for all the clinical facts of parturitional paralysis.

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Dr. Hugh Garland : In an analysis of 15,000 consecutive deliveries at the Leeds Maternity Hospital there were only 19 recorded examples of neurological disorders arising as a result of pregnancy. There are, however, other problems relating to pregnancy which confront the neurologist, and they are possibly more frequent than the complications already discussed.

I propose to discuss these problems under three headings. First, the question of advising as to the possibility of a neurological condition being transmitted to the offspring. Second, the question of pregnancy possibly aggravating an established organic disease. Third, the possibility of a neurological disorder interfering with labour or causing sterility.

THE INHERITANCE OF ORGANIC NERVOUS DISEASE

We can divide inherited conditions into two large groups, namely those where the condition is determined entirely, or very largely, by an inherited factor, and those where there are multiple factors and inheritance only plays a part. The first group

can again be subdivided according to the mode of inheritance and an elementary knowledge of simple Mendelism is essential if mistakes are to be avoided. For example, young Jewish parents had a child who died of amaurotic family idiocy. They sought advice as to the possibility of this happening again, and they were told that there was no risk. The second child died of the same condition. A superficial knowledge of genetics would at least have saved the reputation of the medical adviser in this case. Fortunately, most of the inherited nervous diseases are rare or uncommon.

(1) Certain conditions are inherited as simple dominant abnormalities. Here there will be a history of direct transmission from one generation to the next ; each affected person will have an affected parent, and on the average half the children of an affected person will themselves be affected, irrespective of sex. Further, the disease is in no way transmitted by the normal children. One such condition is Huntington's chorea, which is not very uncommon and is serious, as it almost invariably shows steadily increasing mental deterioration and involuntary movements ; and unfortunately, owing to the late onset, the future victim shows no abnormality until his or her children are already born. My own feeling about this condition is that probably all the children of an affected parent should be advised against marriage, though of course half of these will be perfectly normal individuals. Hypertrophic polyneuritis is inherited in the same way, but in this condition the disability is usually not very severe. The patient can be told that half the children are likely to be affected and that the disease shows no tendency to increase in severity in subsequent generations. Another such condition is von Recklinghausen's neurofibromatosis, but here a difficulty arises owing to the remarkable variation in severity from one case to another. Peroneal muscular atrophy (Charcot-Marie-Tooth) is usually inherited in this way, but sometimes it appears as a sex-linked recessive ; a careful scrutiny of the pedigree will therefore be necessary in each family. Certain cases of myopathy and dystrophia myotonica, and probably familial periodic paralysis, are inherited in the same way.

The problem of recessive abnormalities is more difficult as here the parents are normal, though they may be blood relations, the incidence of consanguinity being higher in the rarer conditions. In these cases, on the average, one child out of four will be affected, though of course all of two or three successive children may be normal or may be affected. The parents can be told the chances are one out of four, or three to one against. Friedreich's ataxia is inherited in this way, and we have all seen several siblings affected with this condition ; other forms of hereditary ataxia usually follow the same rule, as does amaurotic family idiocy, some cases of torsion spasm, Wilson's hepato-lenticular degeneration, and the majority of the myopathies.

In sex-linked abnormalities, such as Leber's optic atrophy, the difficulties are much greater as males are affected, and the defect is transmitted by apparently normal females to half their male progeny.

Finally, there are less well-defined conditions which are certainly inherited, but the exact mode of inheritance is not quite clear ; epiloia is such a condition, though there is evidence that this may be a dominant abnormality ; the cases vary very much from simple adenoma sebaceum or uncomplicated epilepsy, to low-grade idiots with epilepsy and adenoma sebaceum. In these cases it is certainly inadvisable for affected parents to have children.

(2) An entirely different problem is raised by conditions where, at the most, an inherited factor is only one of several. The two most important conditions here are migraine and epilepsy. As an illustration of our uncertainty I should like to mention a recent case in which a young woman who had infrequent fits sought the advice of three neurologists ; the first advised against marriage, the second advised marriage without children, and the third thought the condition could be completely ignored. A tendency to attacks of migraine is certainly inherited as a simple

dominant, and we are all familiar with pedigrees of this type, but migraine is probably never sufficiently serious in itself for any eugenic problem to be raised. Epilepsy is an entirely different problem. All neurologists agree that there is an inherited factor and that a history of affected relations is a common occurrence. Unfortunately published statistics show wide variation, some observers finding the familial incidence as high as 64% (Brown, 1930). Russell Brain (1934), after reviewing the literature, suggests that 10% of the children of epileptics tend to be themselves affected. Paskind and Brown (1936, 1937) pointed out that many of the published figures have been taken from the inmates of colonies for epileptics and defectives, and that in those cases where there is no question of mental defect the family incidence becomes much smaller. They found that in 342 children of idiopathic epileptic parents the incidence of fits was only 0·29%. In a series of 94 cases of idiopathic epilepsy I found a history of epilepsy in the family in 11·4%, but in only 3·2% were both parent and child affected though, for a variety of reasons, this figure may be too low. My own feeling is that in a patient suffering from fits of idiopathic type, with a family history which is completely negative as regards epilepsy, and in the absence of consanguinity, we should advise that the risks are so small that a chance may be taken. The risks, of course, are likely to be much higher if the parents are blood relations. With regard to the relation of epilepsy to migraine the problem becomes more difficult as Lennox (1938) has recently shown that the incidence of epilepsy in families suffering from migraine is two-thirds as great as in those suffering from epilepsy alone, yet probably no one would prevent the marriage of a migrainous subject because of the risk of epilepsy in the children ; this risk, however, is a real one.

The Effect of Pregnancy on Organic Nervous Disease

We are sometimes consulted as to the risk of pregnancy aggravating an already established nervous disease. In my experience, disseminated sclerosis is the most important condition in this group. As in the case of most of the questions raised to-night, the literature contains very little useful information. There are many references to pregnancy increasing disability in disseminated sclerosis, or of actual precipitation of the onset, but they usually refer only to isolated cases. Many of us have seen examples of this aggravation. In the 15,000 deliveries already referred to there were three examples of disseminated sclerosis. One patient developed her first symptom during her third pregnancy ; there was no remission and she became a great deal worse during and after the fourth pregnancy. The second patient had developed the disease prior to her first pregnancy and had improved, but was worse during and immediately after the second pregnancy. The third had symptoms during each of three pregnancies and improved in each case after parturition. I have analysed 100 of my own cases of disseminated sclerosis, but when the men, the spinsters, and the cases of sterile marriage had been excluded, there was only a very small residue. Actually there were 56 females, of whom 35 were married ; of these, 12 marriages were sterile, this giving an incidence of 21% sterile marriage, which is rather high. Further, in 13 cases the disease commenced after the menopause. There were, finally, only eight cases in which pregnancy and disseminated sclerosis overlapped. Of these, six developed signs of the disease during pregnancy or immediately after parturition ; in the remaining two cases, pregnancy had no adverse effect on already established disseminated sclerosis, and in one of the group of six there was a subsequent pregnancy which had no adverse effect. One case was particularly striking in that on the sixth day of the puerperium she first complained of weakness of the arms and then rapidly developed retrobulbar neuritis, paræsthesiæ, and spastic paresis of the legs. After lasting for some weeks the nervous symptoms improved, and there was eventually a complete remission. I therefore feel that there is sometimes an association to the extent that pregnancy occasionally

appears to precipitate the onset of the disease, and that more frequently it tends to increase the disability, though this is not always the case. Again it does not necessarily follow that a relapse, apparently determined by pregnancy or parturition, may not undergo subsequent remission, though presumably every relapse leaves the case of disseminated sclerosis a little worse. A very difficult question arises in relation to the termination of pregnancy. Aggravation may be due to trauma, metabolic factors, or both, but I think that interference may upset the patient as much as labour itself, and that these cases should probably be treated by complete rest and nothing more.

Pregnancy in relation to other diseases does not frequently arise. Most of the degenerative processes arise after the menopause. I have not seen a case of subacute combined degeneration, which is a common disease in the North of England, ever complicated by pregnancy. In the case of neurosyphilis, I doubt whether the disease is ever aggravated by pregnancy; the sterility rate is high, and probably the only feature of importance is that of antisyphilitic treatment. I have no personal experience of pregnancy complicating cerebral tumour, though there are some who think that such cases go downhill rather rapidly. It has frequently been recorded (Tabachnick, 1938) that myasthenia gravis may become worse, or may even commence during pregnancy, though there are also recorded cases of remission during pregnancy. Epilepsy shows similar variation, some cases becoming worse and others becoming better while pregnant. Migraine frequently disappears throughout pregnancy.

Organic Nervous Disease (1) Interfering with Parturition and (2) Causing Sterility

(1) There is little proof that organic cerebrospinal disease ever interferes with parturition. The association of pregnancy with any serious form of paralysis is very uncommon, and I have little personal experience of it. I have seen a very advanced case of post-encephalitic Parkinsonism, with severe paralysis and contractures, give birth to a healthy child without difficulty. Five years ago I saw an advanced case of syringomyelia and syringobulbia with complete flaccid paralysis of the arms and severe spastic weakness of the legs; since that time she has had four apparently normal children, with a normal labour in each case.

(2) In assessing the possible relation of nervous disease to sterility various factors must be considered. In the first place the incidence of involuntary sterility in the general population is not less than 10%. Secondly, in the presence of nervous disease pregnancy may be avoided because of fear of aggravation, or of hereditary transmission. Curiously enough, in Reynolds and Macomber's (1924) textbook on sterility no mention of nervous disease is made. But there can be no doubt that hypopituitarism may produce sterility, amenorrhœa, and loss of libido; usually these are associated conditions, but it is possible that sterility of pituitary origin may precede the appearance of amenorrhœa, even though amenorrhœa is often the first symptom. Hypopituitary syndromes are usually associated with chromophobe adenoma or with increased intracranial pressure causing pituitary compression. Pituitary adenoma is an uncommon condition, and few of us have the opportunity of collecting a large series of cases, but Henderson (1931) has analysed 367 cases from Cushing's clinic from the point of view of sexual dysfunction. He concludes that amenorrhœa and sterility result from the compression of the basophil cells by a space-occupying lesion; for this reason amenorrhœa is an early symptom of intrasellar chromophobe adenoma, existing before expansion of the sellar occurs, and sexual function may remain normal in the case of suprasellar adenoma. In support of this he describes cases where menstruation has returned after sellar decompression and even cases of subsequent pregnancy. Similarly, menstruation may return after operation in cases of acromegaly, and there may be subsequent pregnancy. On the

other hand menstruation may continue in the presence of well-established acromegaly, and it is well known that in such cases pregnancy may occur and that such pregnancy frequently results in an exacerbation of acromegalic symptoms. There are too few recorded cases of pituitary basophilism from which to draw conclusions, but amenorrhœa is usually one of the striking features of this disorder.

Little is known of the relationship between pregnancy and sympathetic disorders, but in some recent experimental work (Simeone and Ross, 1938) it was found that bilateral sympathectomy in cats was followed by an unusually high incidence of abortion and stillbirth even long after the operation. The possibility of a similar effect on the human should perhaps be borne in mind when contemplating bilateral lumbar sympathectomy.

I wish to express my thanks to the Honorary Staff of the Leeds Maternity Hospital and particularly to Mr. G. Blomfield, who kindly analysed the 15,000 cases referred to.

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Mr. W. C. W. Nixon said that though there was a high incidence, about 30% of beri-beri of the wet type in his clinic in Hong Kong, yet the classical polyneuritis of pregnancy was not often seen. In this low incidence he agreed with Dr. Ironside. In one case in which large doses of vitamin B_1 were given from the 30th week until term, there was not a striking improvement until after delivery.

Dr. H. M. Sinclair (Oxford): Dr. Russell correctly mentioned the fact that a high carbohydrate diet increases the requirement of vitamin B_1, but much more important in connexion with this discussion is the fact that pregnancy triples the requirement of the vitamin, and lactation also increases it. This increased requirement, the occasional low values for the apparent vitamin B_1 in blood in pregnancy with and without polyneuritis (Sinclair), the low excretion (Stähler), the response of gestational polyneuritis to vitamin therapy (Strauss and McDonald, and others), and perhaps also the fact that the vitamin is easily destroyed in the gut of people with achlorhydria, all suggest that the symptoms of deficiency of the vitamin are likely to arise during pregnancy. And this has been shown conclusively. For Ogata noticed that beri-beri often appeared during pregnancy; in a series of 107 cases of beri-beri in St. Helena recently reported by P. B. Wilkinson, 41·3% of the women showed a definite connexion between the onset of beri-beri and pregnancy or childbirth. This very high incidence proves that pregnancy and childbirth predispose to the occurrence of peripheral neuritis due to deficiency of vitamin B_1.

Dr. Ironside described the symptoms and signs of polyneuritis following *hyperemesis gravidarum*; of these some are typical of deficiency of vitamin B_1, and some are not (for instance, the vascular changes, and the dysphagia—which might be caused by deficiency of nicotinic acid). Further, Dr. Sheehan said that the vascular changes in Wernicke's encephalopathy were " presumably part of the vitamin B_1 deficiency." Although similar changes have occasionally been described in beri-beri (Bentley) and in deficiency of vitamin B_1 in animals (Prickett), this deficiency is not

generally believed to produce changes in the capillaries of the brain. If Wernicke's encephalopathy is shown to be due to deficiency of a vitamin, it will probably prove to be part of the vitamin B_2 complex.

The great ease with which pure vitamin B_1 can be obtained produces the danger that other vitamin deficiencies will be overlooked in treatment. The requirement of other vitamins is also increased by pregnancy, and therefore it is wise to use preparations, such as yeast, which are rich in vitamins, in the treatment of conditions of doubtful ætiology.

Dr. Purdon Martin said that the discussion had impressed on him the rarity of neurological complications in pregnancy. He doubted whether there was a polyneuritis of pregnancy, although if the vitamin B requirements during pregnancy were three times as great as at other times, perhaps there ought to be a polyneuritis of pregnancy. It must be remembered that pregnancy was not an uncommon condition, and apart from any causal relationship some cases of polyneuritis would occur in association with pregnancy. Was there any evidence that the incidence of polyneuritis was greater among pregnant women than among the general population ? Dr. Ironside had admitted that termination of the pregnancy did not cure the polyneuritis.

Drop-foot following delivery was probably the commonest complication. Chorea gravidarum presented difficult questions, but each case should be considered on its merits, and unless the chorea was very severe the right course was to temporize and see the effects of treatment before advising that the pregnancy should be terminated. Subarachnoid hæmorrhage was perhaps more likely to occur during pregnancy than at other times. Among Dr. Sheehan's fatal cases the severe vascular accidents formed by far the largest group, and we should try and correlate our clinical experience with what he had told us. In the speaker's experience the severe vascular lesions causing hemiplegia were hæmorrhages associated with rising blood-pressure, which he had regarded as a pre-eclamptic condition.

He had been particularly interested in one group of cases to which Dr. Sheehan had referred, viz. the cases of cerebral venous thrombosis after confinement. He had seen four cases in which convulsions came on seven to ten days after delivery ; in each instance the patient, after the convulsions had ceased, was left with hemiplegia from which she had eventually made a good recovery. In his first case, because of blurring of the optic discs, an exploratory operation had been performed, and the surgeon had found a large thrombosed vein on the side of the cerebral hemisphere. He had come to believe that these cases usually made excellent recoveries, and was disappointed that Dr. Sheehan could refer to six fatal cases. Dr. Sheehan's third group of vascular cases was that in which there were numerous punctate hæmorrhages in the cortex and they might be most pronounced in the occipital lobe. The speaker had seen two cases of visual disorientation or loss of visual localization occurring after confinement and had not encountered this symptom otherwise. As it was not met with after gross vascular lesions possibly it was due to cortical lesions such as Dr. Sheehan had described.

Dr. Macdonald Critchley and the **President** also took part in the discussion.

Section for the Study of Disease in Children

President—E. A. Cockayne, D.M.

(*January* 27, 1939)

Osseous Dystrophy.—David Levi, M.S.

Boy, aged 12 years.

Seen at hospital with history of injury to fingers which are deformed. The phalangeal joints are very mobile and the fingers can be pulled into hyperextension. The child has always lived in England. Wassermann reaction negative.

The interest of this case lies in the X-ray appearances of the phalanges and of the femoral heads. There are no changes in the shoulders or skull. The condition is bilateral and there are changes in the 2nd, 3rd, and 4th middle phalanges, and at both extremities of the diaphysis of the first metacarpal of the thumb. Both femoral necks show epiphyseal deformities.

The PRESIDENT said he had read the notes[1] of a similar case recorded by Mr. H. Poston, in the *British Medical Journal*[1] and had brought the plate for comparison with Mr. Levi's skiagrams. Though similar in some respects there were obvious differences, but in one epiphysis in each the resemblance was very great. He thought they might be variants of the same condition and suggested that the title might be changed to epiphyseal dystrophy.

Congenital Cystic Disease of the Lung.—R. S. ILLINGWORTH, M.D. (by courtesy of Dr. DONALD PATERSON).

Male child, aged 3 years 10 months. Birth weight 7½ lb. Breast fed for five months.

History.—Well until an attack of bronchopneumonia in May 1937; he was in a London hospital for this for five months, but no notes about his condition during this period are available. He attended the Out-patient Department of the Hospital for Sick Children, Great Ormond Street, in March 1938, with a history of recurrent coughs and colds since the attack of bronchopneumonia, with some dyspnœa on exertion, and on 13.4.38 he was admitted as a case of bronchiectasis.

On examination (13.4.38).—Pale, ill-looking and apyrexial. Chest: Rhonchi and coarse râles at both bases. Nose: Mucopurulent nasal and postnasal discharge. Early clubbing of fingers and toes. Sputum about 15 c.c. per day on postural drainage: thick, green, rather offensive. Culture: Hæmolytic streptococci and Pfeiffer's bacillus.

Mantoux reaction (1:1,000) negative.

Blood-count: R.B.C. 4,720,000; Hb. 70%. Sedimentation rate 20.

Urine: Sterile.

Skiagrams.—Chest: Signs suggestive of bronchiectasis at right base. Now thought to show congenital cystic disease of the lung. Antra: Opacity of both

[1] *Brit. Med. J.* (1938) (ii), 991, 1061.

antra. Bronchography showed collections of lipiodol in spaces which are probably cysts (fig. 1). Bronchoscopy (Mr. James Crooks): Mucopus seen coming from both right and left lower bronchi.

Pulse, temperature, and respiration rate while in hospital were normal.

The child was sent for three months' convalescence and readmitted on 2.12.38 after an acute pyrexial attack associated with severe coughing.

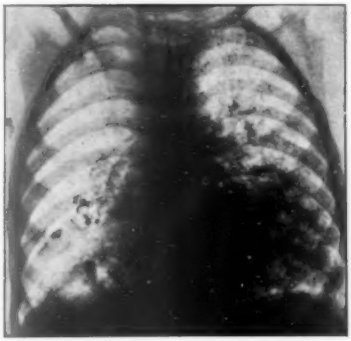

FIG. 1.—Showing pooling of lipiodol.

On examination (2.12.38).—Apyrexial; looked fairly well; had a severe loose cough. Chest: Rhonchi and râles over both sides of the chest. Slight decrease of air-entry at the right base. Clubbing of the fingers as before. Tonsils enlarged with some cervical adenitis.

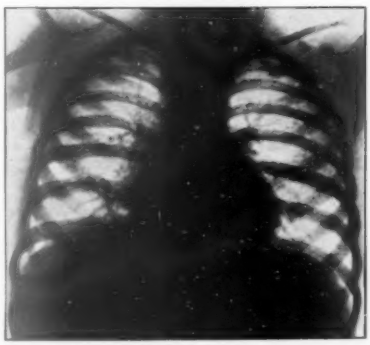

FIG. 2.

Sputum: 30–100 c.c. daily on postural drainage. Cultures.—2.12.38: Hæmolytic streptococci, *Micrococcus catarrhalis*, *Staphylococcus albus*, diphtheroids. 9.12.38: Hæmolytic streptococci, *Staphylococcus albus*. 13.12.38: Hæmolytic streptococci, Pfeiffer's bacillus, *Micrococcus catarrhalis*, diphtheroids. 17.12.38: As on December 13; no tubercle bacilli seen.

Sedimentation rate 23 mm. in an hour.

Skiagrams of chest: Cystic spaces in the right lower lobe (fig. 2).

Treatment: Removal of tonsils and adenoids. Proetz ephedrine replacements for the antritis. Daily postural drainage. Short spell of prontosil treatment (unsuccessful) on account of the bacteriological findings in the sputum.

Progress.—General condition improving. Chest condition unchanged. Sputum: Quantity unchanged.

Discussion.—The PRESIDENT said he had seen many skiagrams of bronchiectasis, but none had shown the dark rings surrounding transparent areas seen in these photographs, and he considered that they were characteristic of congenital cystic disease. He thought that lobectomy would be the correct treatment after the sinuses had been made as sterile as possible.

Dr. PEARSE WILLIAMS had no personal experience of lobectomy in bilateral basal disease, but knew of one child with bilateral basal bronchiectasis in whom lobectomy of the more affected lower lobe almost proved fatal. He feared that such an operation in so young a child would probably lead to spread of infection owing to the altered physical relationships in the thorax. Would it be possible to consider the operation of thoracolysis recently described by O'Shaughnessy and Mason?

The PRESIDENT thanked Dr. Paterson for pointing out how good the prospects of life were in such cases, and would reconsider the proposed operation of bilateral lobectomy in two stages recommended by a thoracic surgeon for his patient. In answer to Dr. Pearse Williams he did not understand why unilateral lobectomy for cystic disease was more dangerous than for bronchiectasis, in which the mortality in selected cases was very low.

Dr. FOSTER CARTER asked why this case could not be one of acquired bronchiectasis rather than congenital cystic disease of the lung, and said it was significant that these cases were almost always associated with a history of pneumonia in infancy. Such a pneumonia frequently gives rise to a massive collapse of one or more lobes of the lung, which then become bronchiectatic. The fact that the cysts fill with lipiodol, and that radiological evidence of collapse is frequently seen in these cases, would also favour a diagnosis of bronchiectasis.

Myeloid Leukæmia.—C. ELAINE FIELD, M.D. (by courtesy of DR. DONALD PATERSON).

Donald H., aged 7 months, was first admitted to hospital December 3, 1938, for treatment of eczema and investigation into the cause of the splenic enlargement, which had been found during routine examination. He is an only child, born at full time; difficult forceps delivery; birth-weight 7 lb. Breast-fed for four and half months, then put on cow's milk. When he was 14 days old his mother first noticed papules under the skin which have gradually spread to a generalized eczematous rash; otherwise he seemed a healthy baby.

On examination.—The child is lively; well nourished, with moderate degree of pallor. The head is square, but no other signs of rickets. The eczema, which at one time extended over the whole body, is now mostly confined to the head and upper part of the chest. Temperature shows periodic rise, once reaching 103° F. Pulse 130 (average). Respiration 30. Abdomen distended. Spleen hard, enlarged 4 in. below costal margin. Liver firm, enlarged 3 in. Heart and chest normal. Glands: Marked general enlargement of occipital, cervical, axillary, and to a lesser extent, of inguinal glands; all are hard and discrete. Tonsils enlarged.

Peroxidase stain: 40% positive, 60% negative. One "blast" cell seen which was oxydase negative.

Supravital stain: No increase of monocytes, large proportion of myelocytes.

Sternal puncture: Active marrow with some monoblasts. Proportion of leucocytes to nucleated reds as 5 : 1.

Fragility of R.B.C.: Complete hæmolysis in 0·33% salt solution, trace hæmolysis in 0·45%. Van den Bergh: Direct reaction negative; total bilirubin a trace.

Wassermann reaction negative. Sedimentation rate 5 mm. in one hour. Mantoux reaction (1 : 1,000) negative.

X-rays: Chest, femur, tibia and humerus all normal.

Investigations

Blood-counts:

8.12.38:		26.1.39:	
R.B.C. ..	2,900,000	R.B.C ..	3,970,000
Hb.	56%	Hb.	74%
W.B.C. ..	48,900	W.B.C. ..	50,700
C.I.	1·0	C.I.	0·9
Platelets ..	272,000 (many abnormally large)	Platelets ..	256,000
Reticulocytes	1·4%	Reticulocytes	1·1%
Differential count:		*Differential count:*	
Polys. ..	21%	Polys. ..	27%
Lymphos. ..	36%	Lymphos. ..	37%
Monos. ..	19%	Monos. ..	20·5%
Eosinos. ..	0·8%	Eosinos. ..	6·5%
Basos. ..	2·5%	Basos. ..	2%
Abnormal cells:		*Abnormal cells:*	
Myelocytes Neutrophil	7%	Neutrophil myelocytes	4%
Myelocytes Basophil	1·5%	Metamyelocytes	1·5%
Metamyelocytes	2·5%	Myeloblasts	0·5%
Myeloblasts	2·5%	Atypical cells	1%
Normoblasts	1·5%		
Macronormoblasts	1·5%		
Megaloblasts	1%		

Well-marked anisocytosis, poikilocytosis, slight polychromasia.

Treatment.—Local application of acriflavine and picis carb. for eczema. No specific treatment.

Progress.—The child's general condition has remained stationary for the last two months.

Comment.—Three diagnoses have been suggested in this case—myeloid leukæmia, monocytic leukæmia and von Jaksch's syndrome. The first was considered to be the most likely on account of the rising white cell count, large liver and spleen and excess of myelocytes in the supravital stain. The duration (two months) does not exclude the condition as remissions can occur even at this age and enlargement of the glands lends support to the diagnosis although they may be a result of septic absorption from the eczema. Age and clinical picture are not characteristic of monocytic leukæmia although the high monocytic count is suggestive. Von Jaksch's syndrome is simulated closely with characteristic age and chronicity, size of spleen and varied blood picture, but there is no evidence of hæmolysis and the reticulocytes and nucleated red cells are low, the white cells rather high—being rarely above 30,000 in this syndrome (Parsons and Hawksley).

In 1918 a similar case to the present one was shown by Paterson as a von Jaksch's anæmia. Later it developed the typical blood picture of myeloid leukæmia proved at autopsy. In 1933 Parsons and Hawksley report another case of von Jaksch's syndrome ultimately dying of myeloid leukæmia.

These facts demonstrate the difficulties which arise in the differential diagnosis of von Jaksch's syndrome and the leukæmias in their early stages, the importance of which lies in any attempt at prognosis.

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Dr. A. G. SIGNY said that he did not think the case was a leukæmia but probably a chronic erythroclastic anæmia as described by Parsons. Against leukæmia were mainly the hæmological findings, as there were not more than 2% of immature cells in any of the given counts. The other points against leukæmia were the facts that there was not a progressive anæmia, nor were the blood-platelets reduced. Further, the bone-marrow smear shown, had no immature myelocytes or myeloblasts, but did show a surprising number of monocytic cells. He thought, therefore, that the diagnosis was that of von Jaksch's anæmia with a possible alternative of a monocytic leukæmia in view of the 30% monocytes in the circulating blood.

Chronic Lymphatic Leukæmia. — JOHN H. COLEBATCH, M.D., M.R.C.P. (by courtesy of Dr. DONALD PATERSON).

R. C., a girl aged 6 years, was first admitted to hospital in September 1937 with a history of progressive pallor and weakness for three weeks. No significant previous history. The mother was said to be "anæmic".

On examination (13.9.37).—Extreme pallor; fever; tonsils enlarged, spleen just palpable. A blood transfusion (450 c.c.) was given at once. Blood-count next day: R.B.C. 1,400,000; Hb. 38%; C.I. 1·3; reticulocytes 0·2%; W.B.C. 13,600 (neutrophil leucocytosis); platelets 140,000. Shortly afterwards the leucocytes fell below 10,000, with a normal differential count.

Subsequent investigations.—Mantoux and Wassermann reactions negative. Red cell fragility: commences 0·45%, complete 0·33%. Red cell diameter (halometer) 7·8 μ. Van den Bergh reaction negative. No excess urobilinogenuria. Fractional test meal: within normal limits.

For the next eight months the child was in and out of hospital. Treatment included a series of blood transfusions at gradually increasing intervals, liver extracts, iron, copper, vitamins B and C, and thyroid, but no lasting benefit resulted. During this period the red cell picture was one of extreme hypoplasia of slowly diminishing severity; the colour-index remained about 1·0, and the leucocytes ranged from 3,000 to 8,000 with the proportion of lymphocytes rising to 75%.

In June 1938, 85% lymphocytes were recorded but primitive cells were only occasionally seen, and the absolute lymphocyte count had not risen appreciably. The spleen was then removed; soft and friable. Weight 120 grm.

Pathological report on section: Enlargement of Malpighian bodies with a diminution of their germinal centres. Definite though slight increase of the lymphoid elements, plus infiltration with lymphocytes. No obvious fibrosis.

There was the usual neutrophil leucocytosis following splenectomy and for two months the rate of fall in hæmoglobin was somewhat depressed. But now the leucocyte count has again fallen to 3,000–10,000, and the number of lymphocytes has risen to 88–99%, with a small proportion of prolymphocytes and some lymphoblasts. The sternal marrow shows an increasing proportion of these primitive cells. The liver is now enlarged and the inguinal glands are readily palpable.

STERNAL MARROW SMEAR (23.1.39).

Myelos.	0	
Neutros.	1·2	
Monos.	0	
Lymphos.	8·6	
Prolymphos.	39·8	98·8%
Lymphoblasts	50·4	

Many smudge cells.
No nucleated reds at all.

LATEST BLOOD PICTURE (23.1.39).

W.B.C.	4,900	
Neutros.	12·5%	
Monos.	0·5	
Lymphos.	72·5	
Prolymphos.	13·5	87%
Lymphoblast	1·0	

Dr. SIGNY thought this was a most important case, as in the early stages nobody could but agree that it presented all the necessary features of an aplastic anæmia, the child never having shown any reticulocytes or response to any therapy. Following the splenectomy there was the usual rise of white cells, and now nobody could doubt that the case was a true lymphatic leukæmia.

This could not, however, be diagnosed from the blood-films but was quite definite from the sternal marrow smear. He did not see, however, why it should be supposed that the case had been a leukæmia throughout its course, particularly as earlier marrow punctures had revealed nothing but rather hypoplastic marrow. He wondered how far the splenectomy could have influenced the course of the disease as the general lymphatic hyperplasia was apparently more marked after the operation.

Jaw-winking in an Infant.—J. N. O'REILLY, D.M., M.R.C.P.

The patient is a male child, aged 6 months. Movements of the left eyelid co-ordinated with the sucking movements of the jaw have been noticed since birth. There is no history of birth trauma, and the child has always appeared well.

On examination.—There is a considerable degree of ptosis on the left side. Sucking movements cause elevation of the left upper lid, which is otherwise motionless. The right side appears normal.

Discussion.—Dr. O'REILLY said that various theories had been put forward to account for this condition. The obvious suggestion that fibres from the 5th nerve nucleus ran in the 3rd nerve seemed improbable in view of their different developmental origins. Bishop Harman had considered that the condition was a throw-back to the fish stage of development, but there were objections to this theory also. No convincing explanation had so far been propounded.

The PRESIDENT thought the condition was very rare. Many years ago he had had a baby with it brought to his out-patient department, and had written a short paper for the *British Journal of Children's Diseases*.[1] He did not believe in the atavistic theory of Bishop Harman. If it were atavistic it should be bilateral, and atavism did not explain the associated ptosis. It was also improbable, as Dr. O'Reilly said, that fibres from the nucleus of the 5th nerve ran in the 3rd nerve, and the fact that a case had been reported, in which the condition was acquired in middle age, could not be explained on this hypothesis. He did not think that any explanation offered was satisfactory.

Streptococcal Bacteriæmia.—HAROLD WATTS, M.B. B.S. (introduced by Dr. DONALD PATERSON).

Reginald T., aged 6 years.

13.11.38: Admitted to hospital with seven days' history of fever, sweating, and earache. Three days before the onset of symptoms he sustained a punctured wound of a finger which healed by first intention.

Past illnesses.—November 1937, microcytic anæmia considered to be due to chronic tonsillitis. At this time the spleen was easily palpable. Blood-count: Hb. 64%; R.B.C. 4,020,000.

Personal history.—The child has never been abroad. One brother, aged 4, is in good health.

On examination.—A pale thin child with a considerable degree of proptosis. Spleen enlarged ½ in. below the costal margin. Some inflammation of both ear-drums around the handle of the malleus. Auscultation of the heart revealed a soft systolic murmur at the apex. No clubbing of fingers. No petechial hæmorrhages seen in the skin.

Skiagram of chest: No miliary deposits seen.

Wassermann and Kahn reactions negative.

Blood-cultures.—15.11.38: A pure growth of hæmolytic streptococci in fifteen hours. 19.11.38: Sterile.

No agglutination to typhoid, paratyphoid A and B, or *B. abortus*.

Urine: Culture sterile. No red cells seen in several specimens.

Throat swab: Staphylococci and *Micrococcus catarrhalis*.

[1] *Brit. Journ. Child. Dis.* (1914), **11**, 352.

Blood-counts	R.B.C.	Hb.	W.B.C.
14.11.38	3,400,000	68%	2,400 (Polys. 48% ; lymphos. 49% ; monos. 2% ; eosinos 1%).
18.11.38	—	58%	20,700 (Polys. 78% ; lymphos. 19% ; monos. 2% ; basos. 1%.)
22.11.38	—	60%	10,900 (Polys. 56% ; lymphos. 44%.
23.11.38	—	76%	7,000 (Polys. 69% ; lymphos. 20% ; monos. 7% ; transitional myelocytes 3% ; myeloblasts 1%).
29.11.38	—	76%	10,500.
7.12.38	—	76%.	
19.1.39	4,500,000	80%	7,000.

Treatment.—17.11.38–18.11.38 M & B 693 for forty-eight hours. Total dosage 2·25 grm. 19.11.38–28.11.38 Proseptasine for nine days. Total dosage 15·25 grm. Blood transfusion of 400 c.c. on 22.11.38.

Commentary.—The most striking feature of the case is the fact that in spite of a high swinging temperature the child never looked ill and did not complain of anything while in hospital.

M and B 693 was discontinued after 48 hours because response to treatment appeared to be inadequate. From 25.11.38 till 28.11.38 there was an evening rise of temperature to 103° F. This was considered to be a "prontosil" fever and proseptasine was discontinued. There have been no further rises of temperature.

On examination.—19.1.39 : Still rather pale but Hb. 80%.

No murmurs heard over the præcordium. The spleen is easily palpable.

Dr. SIGNY thought that the difference between bacteriæmia and septicæmia was only one of degree. In the latter, the patient usually presents himself as a fulminating case with high swinging temperatures, as did this particular patient. He thought a striking feature of the case was the early depressed leucocyte count as the patient, with only 2,400 cells after a seven-day fever, would be considered to have an extremely unfavourable prognosis, yet the child was not particularly ill and after four days of specific treatment the white cells had rapidly risen to 20,000 per c.mm.

Dwarfism of Uncertain Causation.—F. PARKES WEBER, M.D.

The patient, R. S., a boy, aged 13 years, was brought to hospital in June 1938, because his father was anxious about his short stature. There is no history of dwarfism or infantilism in the family, and the boy's weight at birth was 3·5 kg. (7½ lb.). The patient is the only child (the mother has never been pregnant otherwise). Except for the patient's small size (height 115 cm. ; weight 20·4 kg.), and that the bridge of his nose was rather depressed and broad, and that by X-ray examination the pituitary fossa appeared rather small, there was nothing abnormal to be discovered by ordinary examination. The osseous, sexual and mental development corresponded with the boy's age. By November 1938, without special treatment, his size had increased (height 121 cm., weight 23·5 kg.). The blood-serum gave negative Wassermann and Meinicke reactions. No enlargement of spleen or liver.

Blood-count : R.B.C., 4,020,000 ; Hb. 79% ; W.B.C. 8,300 (basos. 2% ; eosinos. 4% ; polys. 68% ; lymphos. 17% ; monos. 9%). Blood-sugar (fasting) 0·82%.

It is probable that the boy will develop fairly normally, except for some smallness of stature.

CORRIGENDUM.

"PROCEEDINGS," 1938, 32, 320 (Sect. for the Study of Disease in Children, 16).

Line 18 (Dr. Parkes Weber's remarks in discussion on a case of Congenital Steatorrhœa with Congenital Morbus Cordis) *for* "Dr. K. Fürth had investigated and described this condition . . ." *read* "Dr. K. Fürth had investigated, but did not describe this condition . . ."

Section of Odontology

President—A. H. Parrott, O.B.E., M.D.S.Birm.

[*January* 23, 1939]

Calcified Tissue of Repair

By E. Wilfred Fish, M.D., D.D.Sc., D.Sc.

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I.—Introduction

This paper is not directly concerned with the gross phenomena of the healing of fractures in bone, but more generally and more minutely with the mechanism by which the cells associated with the hard tissues of mesenchyme origin repair the calcified collagenous matrix.

The investigation was originally confined to the repair of lesions in the dentine and cementum, but the cells concerned in the reactions were found sometimes to be derived from the undifferentiated mesenchyme of the bone. All three tissues were, therefore, brought under observation, and indeed there does not appear to be any fundamental difference in the reactions to injury of these three varieties of hard tissue other than those inherent in their morphological differences, vascularity, and the accessibility of the matrix to the cells.

In the course of this investigation 110 pathological specimens, selected for their special bearing on the subject, have been serially sectioned and examined, and 940 experimental operations have been performed on the teeth or bones of monkeys, dogs, guinea-pigs, and rabbits. The purpose of these operations was to inflict either mechanical or toxic injury on the bone dentine or cementum, and to observe the reaction of the mesenchyme cells to the irritation thus produced.

Except where ground sections were made, the affected tissues in each case have been serially sectioned and stained with hæmatoxylin and eosin and with van Gieson alternately, the latter proving invaluable for differentiating new deposits of collagen. Gram sections have also been included in the series where necessary. In each type of experiment direct examination of the tissues has been made by means of fresh or stained ground sections. This method of examination was found to be indispensable.

Some part of the material has already been described since it had a direct bearing on the pathology of the bone (Fish, 1939 (i) dentine, *id.*, 1931, 1932, 1939 (i)), or the parodontal tissues (*id.*, 1935). The reactions then recorded are now considered from a different aspect, however, and in the light of further experiments, in order that the activities of individual cells may be described rather than the cumulative effect of such activities on the welfare of the animal as a whole. Additional material, prepared for the purpose of an investigation into the effects of avitaminosis C on the teeth of guinea-pigs (Fish and Harris, 1934) has been re-examined, and a number of further experiments based on those earlier findings have been performed.

It was found that when the hard tissues of mesenchyme origin are disturbed two distinct types of reaction may be observed which result in the production of two entirely different varieties of calcified tissue of repair. One of these varieties, for which the specific phrase "*calcific repair tissue*" will be reserved, resembles lacunar cementum and bone, but the other, which will be called "*calcific scar tissue*," is unlike any of the normal hard tissues of the body. The general phrase, "calcified tissue of repair", which is used in the title, will be taken to include both these varieties.

The first kind, calcific repair tissue, is formed when the *undifferentiated* mesenchyme cells associated with bone or dentine are submitted to abnormal stimuli of a certain definite strength which must, however, fall very far short of causing them to degenerate or die. Calcific scar tissue, on the other hand, is formed when the already *differentiated* cells of mesenchyme origin, that is, the odontoblasts and perhaps the osteoblasts, are irritated to such a point that they do degenerate and even disintegrate and actually die.

Calcific repair tissue may, therefore, be seen on the outskirts of an infective lesion of bone or of the dental pulp (Fish, 1939 (i)); also after aseptic surgical interference with bone, dentine, or cementum, it will be observed filling up the Howship's lacunæ as soon as the injured surface has been absorbed by osteoclasts.

There are, however, several points in which this calcific repair tissue differs from both bone and cementum: and the attempt to identify it with either or with any normal tissue has proved to be confusing and of no constructive value. The commonest example of calcific repair tissue is the early callus of a healing fracture, but there are other examples with distinguishing features even from callus, which seem to require a term with a wider application.

The second type of calcified tissue of repair "calcific scar tissue" is found almost exclusively as a response to injuries of the dentine and dental pulp. It does not resemble morphologically any normal tissue of the body, although it consists of a calcified collagenous matrix which reacts to every test in the same way as that of bone or dentine.

The essential difference of this tissue from the normal hard tissues of the body and from the calcific repair tissue just referred to is that it does not at any time contain any living cells or cell processes at all, and that it is, therefore, either hyaline and in ground section apparently homogeneous and structureless, or, alternatively, it may contain the debris of the damaged odontoblasts and other cells in the vicinity of the injury or degenerative processes which caused its production. The other distinguishing feature of this type of tissue is that it only forms amongst fully differentiated hard tissue cells and possibly indeed only amongst odontoblasts which are actually degenerating and undergoing dissolution. Familiar examples are the hyaline barrier between primary and secondary dentine (Fish, 1932) and the amorphous calcified mass which seals up the pulp chamber at the senile end of a guinea-pig's tooth (Fish and Harris, 1934).

The calcified tissues of repair will, therefore, be described under these two headings of "calcific repair tissue" and "calcific scar tissue". The calcific repair tissue group will be further subdivided by recording both the observed examples and also

those experimentally produced, as they appear, first in the pulp, then in the periodontal membrane and then in association with bone apart from the teeth.

II.—Calcific Repair Tissue

In order to appreciate the biological status of calcific repair tissue it is necessary to refer to the anatomical arrangement of the cells in normal bone and in lacunar cementum, and to consider its significance. In the former the flattened cells are arranged in cylindrical laminæ surrounding a blood-vessel, and in this way form the Haversian systems (fig. 10). Their numerous canaliculi are approximately parallel to each other and all anastomose freely. They run at right angles to the laminæ so that they extend radially out into the calcified matrix from the blood-vessels and not only irrigate the matrix, thoroughly hydrating its colloidal content, but provide a very adequate means of supplying tissue fluid to the osteocytes which thus can live imprisoned in the otherwise relatively impermeable matrix for years.

Lacunar cementum, on the other hand, shows no regular arrangement of the cells. Many of the spider-like canaliculi do not appear to intercommunicate at all, and at best only serve to irrigate small areas of the matrix (cp. fig. 6). Moreover, as might be expected, cells often die in the depth of the cementum and disappear by autolysis (Ross, 1933).

This difference between the cell pattern of bone and that of cementum is most obvious in ground sections. Nevertheless, although the canaliculi are not well shown in decalcified sections, typical specimens of the two tissues may still be distinguished since the lacunæ are more irregular in shape and position, and on the whole are larger in cementum than in bone.

Calcific repair tissue may present the appearance of either lacunar cementum or bone or indeed any intermediate phase quite without reference to the situation in which it is found, whether it be in the pulp, in the parodontal tissues, in bone, or in neoplastic growths of mesenchyme origin. In the most irregular specimens there may even be two or more cells in the same lacuna, or again the cells may have died and the lacunæ be empty. The significance of this pleomorphism will be considered in the discussion after the various examples observed or experimentally produced have been described. It will be suggested that it indicates a recessive or atavistic tendency on the part of the hard tissue forming cells under the stress of abnormal stimulation.

(1) *Calcific Repair Tissue in the Pulp Chamber*

(*a*) *Observed examples.*—It has been shown that chronic or subacute inflammation of the pulp is commonly associated with absorption of the dentine (Fish, 1932). If the absorption becomes excessive a condition is produced which has long been known as " pink spot " (Pritchard, 1931). It is more usual, however, for the absorbed matrix to be replaced to some extent by calcific repair tissue.

In a case already briefly described (Fish, 1939 (i)), and further illustrated in figs. 1 and 2, it was shown by analogy with bone, that both the absorption of the dentine by osteoclasts and the production of this new calcific repair tissue were due to the undifferentiated mesenchyme cells being irritated to a varying extent by toxic matter diffusing into the surrounding tissue from a focus of infection in one cornu of the pulp.

Where the concentration of toxic matter was more intense osteoclasts were produced and absorbed the dentine. Further afield, where dilution of the toxic matter by tissue fluid had occurred, constructive cells appeared and built calcific repair tissue. The precise degree of toxic stimulation to which the mesenchyme cells were submitted was shown to be the determining factor. This characteristic response of the mesenchyme associated with bone and dentine to varying degrees of toxic irritation appears to be a very constant feature (Fish, 1939 (i)).

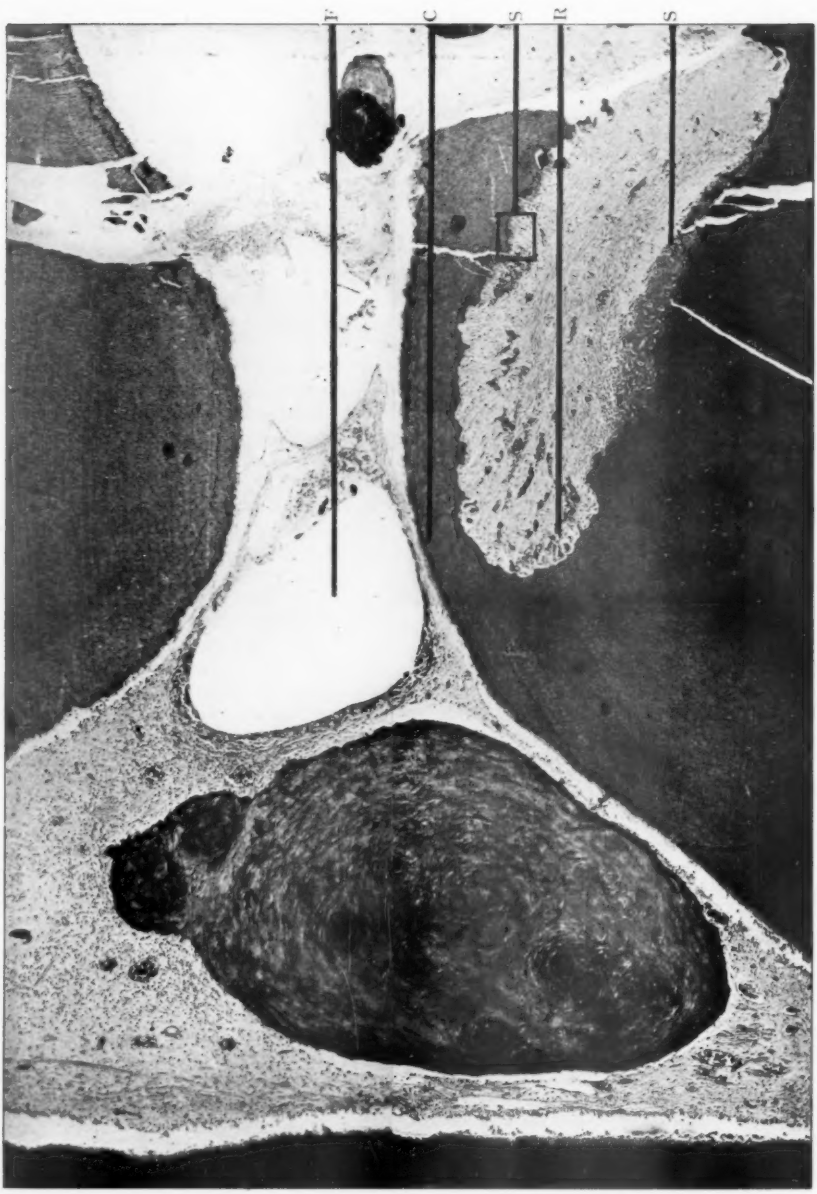

FIG. 1.—Photomicrograph × 53 of a decalcified section of the pulp of a human molar showing reaction to subacute infection.
F = zone of infection ; C = zone of contamination ; R = zone of irritation ; S = zone of stimulation.

Fig. 1 indicates the part played by toxic irritation in this reaction ; a subacute abscess of the pulp at (F) constitutes the zone of infection, to which the actual germs are all confined by polymorphonuclear leucocytes ; (C) is the zone of gross toxic contamination, (R) is the zone of irritation and dentine absorption, and (S) is the zone of stimulation and calcific repair tissue production. Fig. 2 illustrates the type of calcific repair tissue which is being formed in response to the stimulus. From the size and arrangement of the lacunæ it may be inferred that a ground section of this tissue when the reaction was complete would have resembled fig. 6, showing the spiderlike arrangement of the canaliculi ; but as the tissue is being formed in the pulp it can hardly be called cementum, and still less bone. This specimen was kindly sent to the laboratory by Mr. Guy Ash.

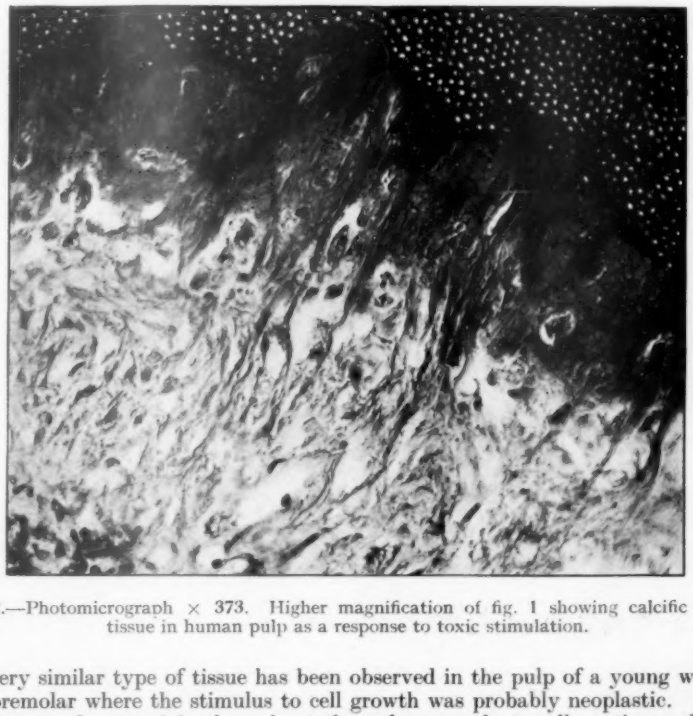

Fig. 2.—Photomicrograph × 373. Higher magnification of fig. 1 showing calcific repair tissue in human pulp as a response to toxic stimulation.

A very similar type of tissue has been observed in the pulp of a young woman's lower premolar where the stimulus to cell growth was probably neoplastic. All the cells of mesenchyme origin throughout the pulp were abnormally active and osteoclasts, osteoblasts, and fibroblasts, had appeared in great profusion, so that the pulp presented a typical picture of localized osteitis fibrosa.

This specimen will be described in more detail elsewhere but fig. 3, which represents part of the very greatly enlarged pulp chamber, shows the Howship's lacunæ at the absorbed edge of the dentine filled with calcific repair tissue of a very primitive cementum type in which the cell lacunæ are large and irregular and most of them empty, the cells having disintegrated. The hard tissue on the left of the picture which lies free in the pulp is slightly better organized and more like bone ; the cells in it are alive, and it is laid down irregularly throughout the whole extended pulp chamber.

The stimulus to the undifferentiated mesenchyme in this case must be called, for lack of specific knowledge, a neoplastic " urge ", but that it falls into the category

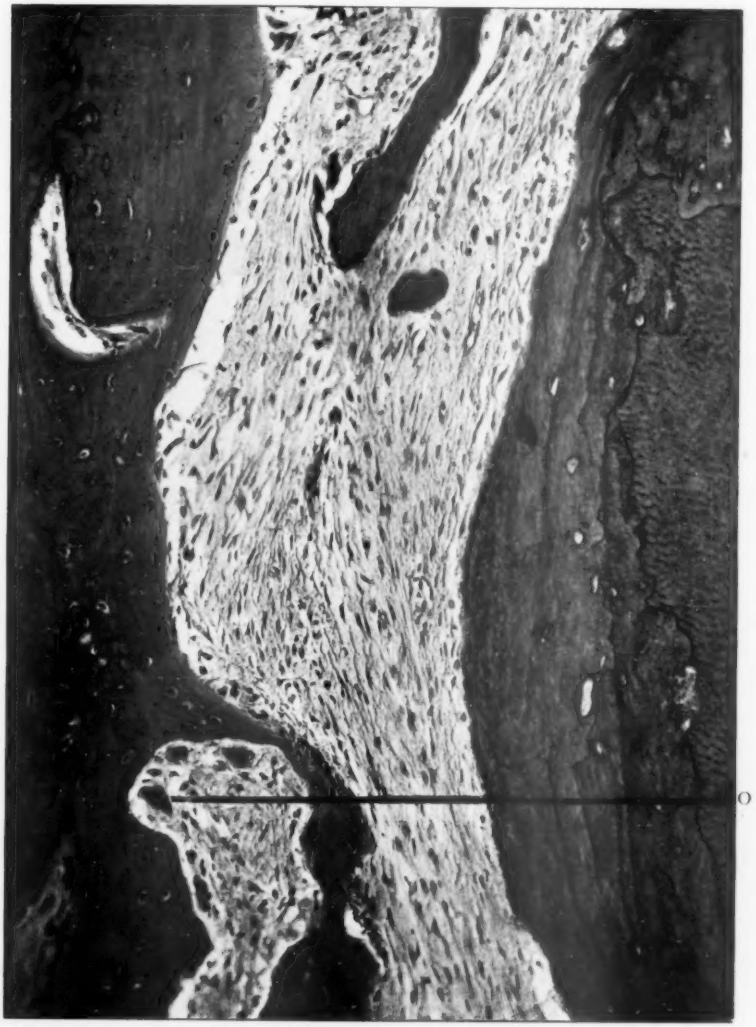

FIG. 3.—Photomicrograph × 177 of a decalcified section of the pulp of a human tooth showing a condition indistinguishable from osteitis fibrosa. Calcific repair tissue appears as a neoplastic response.

of neoplasms is shown by the disordered activity of all the mesenchyme cells, by the proliferation of fibrous tissue, and by the appearance of numbers of osteoclasts (O) which are continually eating away the calcific repair tissue as soon as it forms ; yet

the actual hard tissue built under these conditions by the mesenchyme cells closely resembles that produced when the stimulus was toxic in character (cp. figs. 2 and 7, and Fish, 1932, fig. 55) or mechanical (cp. fig. 4).

(*b*) *Experimental examples.*—It has frequently been observed under particularly severe experimental peripheral injuries of the dentine, especially if heat is generated in the grinding, that all the odontoblasts break up and are replaced by polymorphonuclear leucocytes and lymphocytes. Some weeks later, if the experiment be

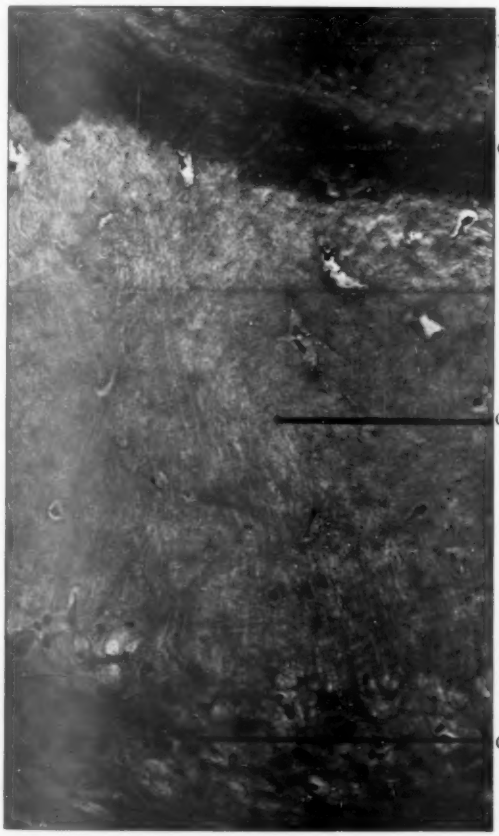

FIG. 4.—Photomicrograph × 280 of a decalcified section showing calcific repair tissue in the pulp of a monkey's tooth—experimental reaction to mechanical irritation (sixteen weeks).

prolonged and the pulp recovers, typical calcific repair tissue is deposited on the pulp surface of the dentine, corresponding in position to the peripheral injury (Fish 1932, fig. 35A).[1]

A more extensive deposit is often obtained in response to mechanical irritation

[1] At that time the author, with a simpler creed, referred to it as "Calcific Scar Tissue" which should now read "Calcific Repair Tissue".

by actually exposing the pulp aseptically. Fig. 4 shows the result of such an operation. The pulp of a monkey's canine was opened through the dentine of the crown, and a fine sterile probe was passed down the canal grazing the wall and injuring both the odontoblasts and the neighbouring cells. The exposed pulp was covered with sterile vaseline under a metal cap, and the opening in the dentine was closed with cement and left for sixteen weeks.

The sections showed that first a layer of calcific scar tissue (C.S.T., fig. 4) formed amongst the disintegrating odontoblasts (cp. fig. 18) and was deposited on the denuded

FIG. 5.—Photomicrograph × 14 of a ground section of a human tooth showing absorption from the periodontal membrane.

dentine (D). Later on, when the debris had been cleared up by phagocytes, a group of regular oval cells, each with a single well-defined nucleolus, began to form a deposit of calcific repair tissue (C. R. T.). Some of these cells may still be seen at the edge (C), while others now occupy the large irregular lacunæ in the calcific repair tissue matrix. The calcific repair tissue ceases to be formed when the surrounding tissues have completely resumed their normal healthy appearance.

(2) *Calcific Repair Tissue taking Origin from the Periodontal Membrane*

(*a*) *Observed examples.*—It is a common observation to find small areas of absorption at various points in the cementum of a tooth. These areas are also quite often repaired by a tissue which exactly resembles and is naturally referred to as lacunar cementum, though it is often the hyaline and not the lacunar cementum which was absorbed in the first place, and the repair tissue lies as an isolated islet of lacunar cementum, surrounded by dentine, hyaline cementum, and periodontal membrane.

It is less common, but not extremely rare, to find that the absorption has continued into the dentine until it perforates the pulp chamber. The lesion, which can be recognized radiographically, progresses for a number of years without, as a rule,

FIG. 6.—Photomicrograph × 222. Higher magnification of fig. 5 showing calcific repair tissue in the pulp chamber. Neoplastic or toxic response.

giving rise to urgent symptoms; clinical cases have been under observation for over three years, and only in one did an acute abscess of the pulp supervene.

This absorption of the cementum and dentine may be associated with the diffusion of soluble toxic matter down the periodontal membrane from the parodontal sulcus, whereupon replacement and absorption alternate as the toxic tide ebbs and flows. In addition to this, however, there must be some abnormal sensitivity of a particular small group of cells, since the lesion is localized and rare. Some pathologists might prefer to regard it frankly as an osteoclastoma which also contains some constructive cells, but the point is not material to the present paper. Figs. 5, 6, and 7, illustrate two cases.

Figs. 5 and 6 are photomicrographs of a ground section of such a tooth, and show that the pulp chamber had been widely opened up and enlarged by osteoclasts. At one point calcific repair tissue has been laid down in what must have been, on the toxic hypothesis, a backwater of the toxic tide (cf. Fish 1939, (ii)). This new tissue exactly resembles lacunar cementum, but it must not be overlooked that it appears

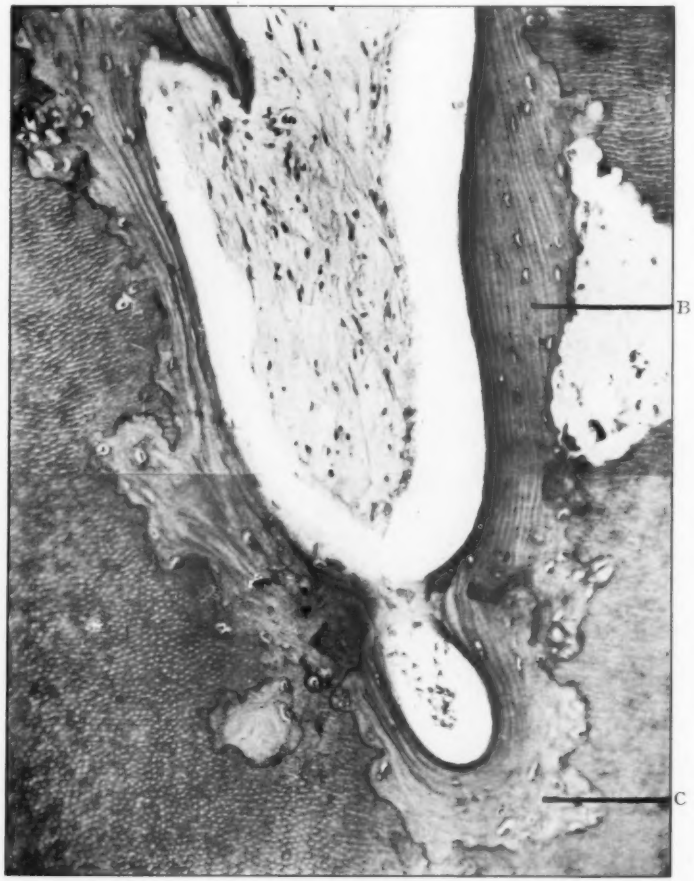

FIG. 7.—Photomicrograph × 163 of a decalcified section of a human tooth showing absorption and calcific repair tissue from the periodontal membrane. Neoplastic or toxic response.

in the pulp chamber on the pulp surface of the dentine. This is, of course, definitely ectopic, and makes it difficult to call it cementum or to regard it as being associated with any previously differentiated cementoblasts.

Fig. 7, taken from a decalcified section of a similar tooth, shows the replacement of considerably more of the dentine lost by absorption, but in this case part of the

calcific repair tissue exhibits typical lamellæ (B) and appears to be identical with " coarse fibre " bone, such as is seen in osteitis fibrosa. Elsewhere the repair tissue is of the usual, less organized, type, and closely resembles lacunar cementum (C). The lacunæ in this latter variety are often empty, the cells having died, while in the better-organized part (B) they generally survive.

(*b*) *Experimental examples.*—It has already been shown that an experimental injury to the cementum of a monkey's tooth produced aseptically by a dental bur was filled up with a deposit of calcific repair tissue (Fish, 1935). This repair tissue resembled lacunar cementum, and inasmuch as it served to attach the periodontal fibres to the tooth and refrained from becoming ankylosed to the bone it was functioning precisely as cementum normally does. The tissues which had been injured, however, were hyaline cementum and dentine, so that the question arose whether the new tissue was in fact lacunar cementum or merely another example of calcific

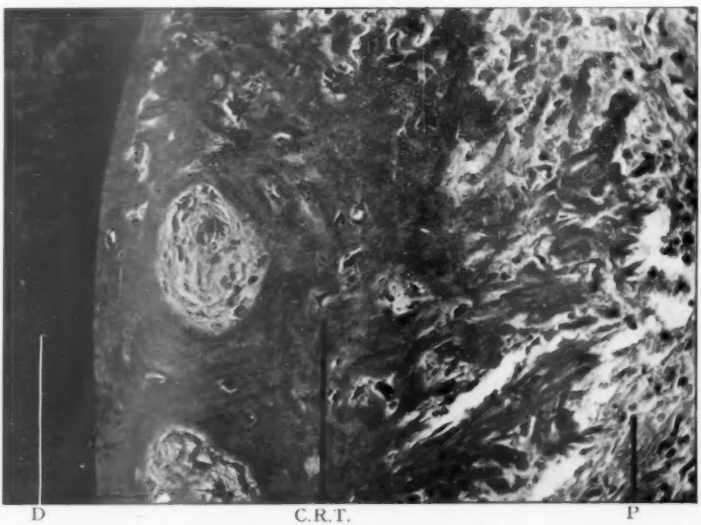

FIG. 8.—Photomicrograph × 280 of a decalcified section after surface injury to the root of a rabbit's tooth showing calcific repair tissue derived from the periodontal membrane. Experimental reaction to mechanical irritation (six weeks).

repair tissue. It was, of course, only a point of academic interest, since the anatomical distinction between the two tissues is so fine as to defy detection, if indeed any difference exists at all.

When, however, a similar injury was inflicted on the side of a guinea-pig's tooth or a rabbit's tooth (fig. 8), the calcified tissue of repair (C. R. T.) was still of exactly the same type, that is, it had spider-like lacunæ (fig. 9), did not become attached to the bone, and served to attach the periodontal fibres (P) to the denuded dentine of the tooth (D). It was, nevertheless, very difficult to describe the tissue in this new series of experiments as lacunar cementum, because neither the rabbit nor the guinea-pig has any such tissue in its body, nor presumably can it have had any biological experience of such a tissue in the course of its evolution. On the other hand the lacunæ have not the shape or arrangement of bone lacunæ, and the failure of the tissue

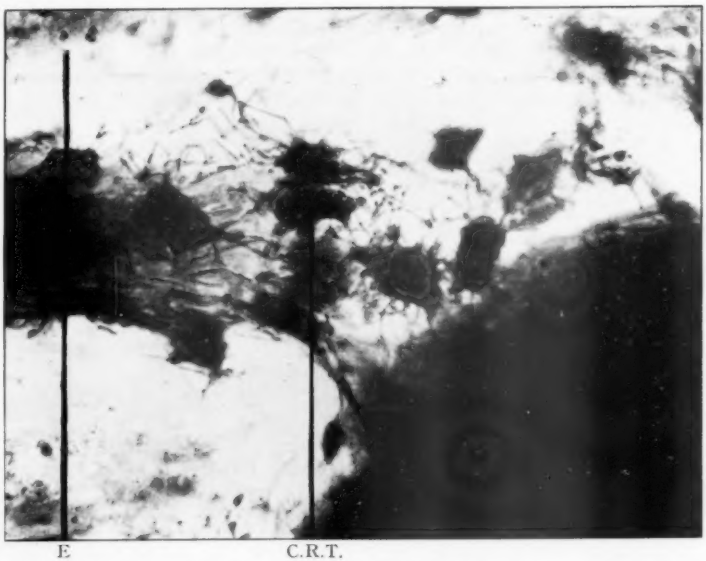

FIG. 9.—Photomicrograph × 400 of a ground section after surface injury to the root of a guinea-pig's tooth showing young calcific repair tissue derived from the periodontal membrane. Experimental reaction to mechanical irritation (six weeks). E = injured edge of dentine and C.R.T. = calcific repair tissue.

FIG. 10.—Photomicrograph × 280 of a ground section of normal mammalian bone (ox).

to join up with the ordinary alveolar bone in both primate and rodent is a further mark of differentiation.

(3) *Calcific Repair Tissue in Bone*

(*a*) *Observed examples.*—Calcific repair tissue is very frequently observed in bone, and indeed any form of irritation will normally produce a specimen at some point in the region of the lesion. Examples have been observed and also produced experimentally in cases of fracture, bone infection (Fish, 1939 (i)), and aseptic surgical interference (fig. 14).

A tissue which might quite well be described as calcific repair tissue is also found in neoplastic changes in bone. Fig. 11 depicts a ground section of human mandible, exhibiting localized osteitis fibrosa. The decalcified sections of the same growth

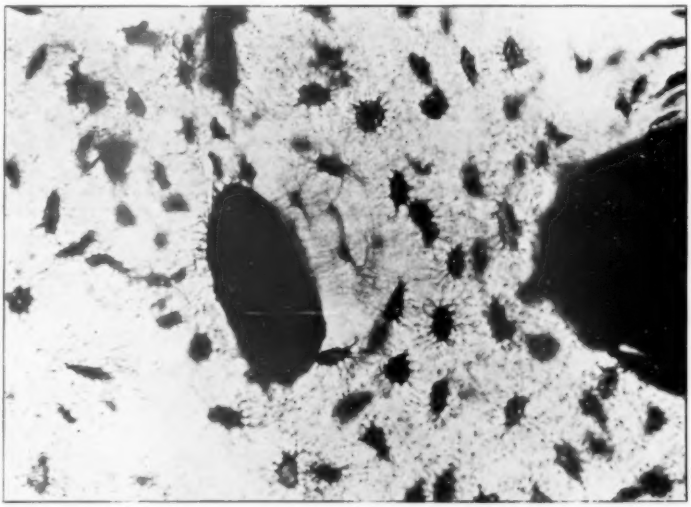

FIG. 11.—Photomicrograph × 280 of a ground section of human bone in osteitis fibrosa.

exactly resemble fig. 3, except of course that no dentine is present. As in the tooth pulp, all the cells of mesenchyme origin are produced in excessive numbers and stimulated to abnormal activity which is of no service to the individual. The new tissue is of exactly the same type, and as fig. 11 shows, it seems to represent an intermediate stage between bone and cementum, or between primitive and mammalian bone (cp. figs. 10 and 21). Osteoclasts are perpetually digesting out the organic matter of the new calcified matrix, and indeed of the surrounding bone. The lime salts are set free and typical Howship's lacunæ appear, which in turn become filled in with new calcific repair tissue (cp. Fish, 1939 (i), fig. 4B). Meanwhile the fibroblasts are equally active.

Fig. 12 shows a ground section of an ivory exostosis of the jaw removed by Mr. Dudley Buxton. The type of " bone " is similar to that in osteitis fibrosa, though on the whole better organized, and of course there is no fibrous tissue and very little absorption. Part of the tumour is indeed typical Haversian bone, but in other

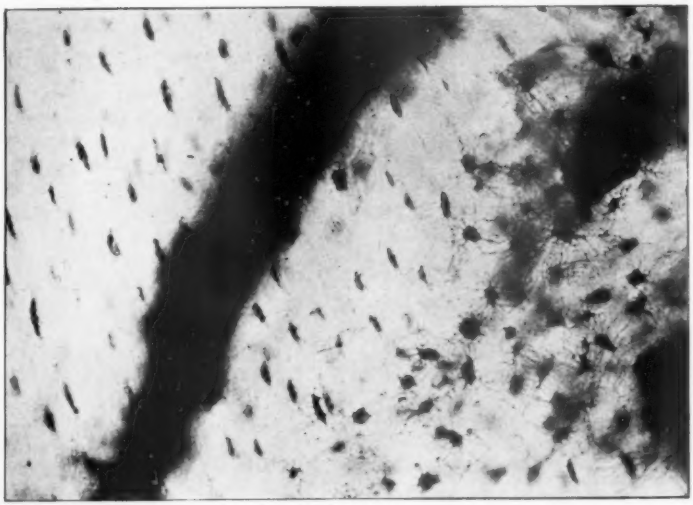

FIG. 12.—Photomicrograph × 200 of a ground section of human bone from an ivory exostosis.

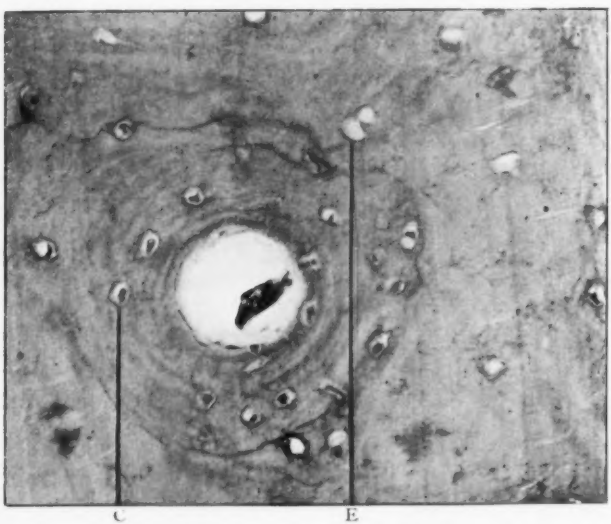

FIG. 13.—Photomicrograph × 350 of a decalcified section of human bone from an ivory exostosis. C = osteocytes; E = empty lacunæ.

places it resembles cementum and is almost indistinguishable from reptilian bone (cp. figs. 12 and 21). The decalcified section (fig. 13) shows that many of the cells were dead, presumably because the tortuous canaliculi could not provide adequate nourishment or drainage. It is constantly observed in such tissue that only the lacunæ near the blood-vessels contain cells, and that the more distant ones are empty.

(*b*) *Experimental examples.*—When septic infection is introduced experimentally into a bone the organisms are confined, as in other tissues, to the immediate vicinity of the site of implantation by leucocytes. The reaction corresponds exactly to that shown in figs. 1 and 2. Soluble toxic matter diffuses out from the infected area and contaminates the surrounding tissues killing the cells. At a certain distance from the source, where this toxic matter has become more dilute, so that the osteocytes and fibroblasts can survive, it causes the production of osteoclasts. Further on, the still more dilute irritant stimulates the mesenchyme cells to form new bone or callus

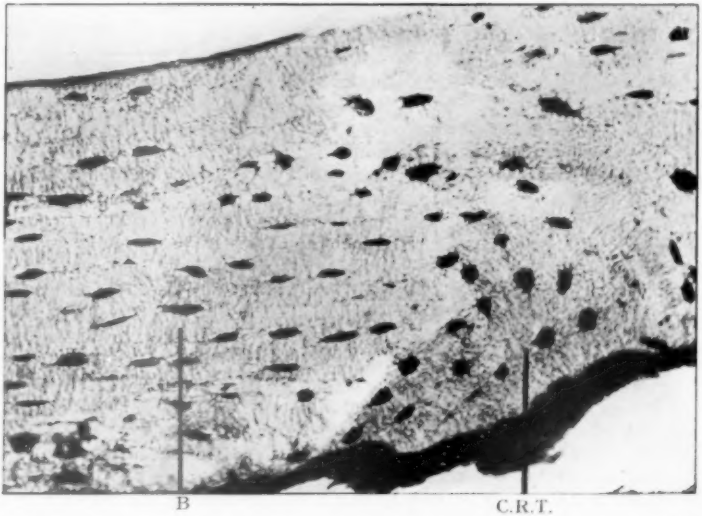

FIG. 14.—Photomicrograph × 280 of a ground section showing calcific repair tissue at the site of amputation of a guinea-pig's tibia (twelve weeks).

(Fish, 1939 (i), fig. 3D). The callus thus formed, however, is exactly the same material as was seen in the pulp (figs. 2 and 4), and very similar to that in figs. 11, 12, and 13.

Fig. 14 shows a ground section of the callus which has formed round the end of the tibia of a guinea-pig, where the leg had been amputated three months before the animal was killed. It indicates the primitive cementum-like appearance of this deposit (C. R. T.) in comparison with the remnant of the shaft of the bone (B), thereby identifying it with the other examples of calcific repair tissue which have been described. When, however, a leg had been fractured instead of amputated, the stimulus of function caused osteoclasts to remove this irregular callus and osteoblasts to replace it at leisure with well-organized and presumably stronger Haversian bone.

III.—Calcific Scar Tissue

It has, therefore, been shown how consistently this primitive type of bone or "calcific repair tissue" is produced whenever the undifferentiated mesenchyme cells of either bone, periodontal membrane, or of the pulp are irritated. When, however, fully differentiated odontoblasts, which are actually engaged in depositing or maintaining the dentine, sustain an injury which causes them to degenerate in situ, an entirely different variety of calcified tissue of repair is formed which exhibits no cell pattern at all in the matrix.

If these cells are only slightly irritated and do not degenerate they react, as might be expected, by an accelerated production of perfectly normal dentine. This reaction is commonly seen under the translucent zone of a carious human molar. Sometimes there have been several periods of increased activity each time the translucent zone was repaired, after being penetrated by the advancing caries. The history of these periods of cell activity is permanently recorded in the texture of the dentine (Fish, 1932).

It frequently happens, however, that the odontoblasts are so badly damaged that they shed their fibrils and degenerate, and a proportion of them actually die. This occurs when caries attacks the teeth in almost any situation other than the occlusal surface of the molars, and can also be produced experimentally.

Figs. 15 A, 15 B, and 15 C, are photomicrographs of three parts of the odontoblast layer of a monkey's tooth. An experimental cavity had been drilled half way through the dentine of the crown forty-eight hours before the tooth was extracted. Fig. 15 A shows the odontoblasts under the deepest part of the cavity. Each of these cells had suffered amputation of half its fibril at the time when the cavity was cut; it thereupon cast off the remainder of its fibril, degenerated, and was rapidly breaking up. There was, however, already after only forty-eight hours, a deposit of collagenous matrix (M), on the surface of the dentine and in the tissue fluid round these degenerating and dying cells. This deposit is the homogeneous layer of calcific scar tissue which ultimately separates the dead primary dentine from the new secondary dentine (Fish, 1932, and fig. 15 D).

Fig. 15 B shows the odontoblasts under a shallower part of the same cavity. These cells had suffered less severely, and though they had shed their damaged fibrils they might have recovered and developed new ones which would have appeared later in the secondary dentine (cp. fig. 15 D). Meanwhile these cells have not formed so much calcific scar tissue (M) as those which were more severely damaged. Other cells (D) which had not even shed the remains of their fibril and only show that they have been injured by some slight distortion in shape, had formed no new matrix at all; these odontoblasts would not have formed a homogeneous zone of calcific scar tissue but would have made some addition to the primary dentine as already described. Fig. 15 C shows some normal cells from under the adjoining uninjured dentine for comparison.

Fig. 15 D shows a ground section of the end-result of a similar reaction twelve weeks later. The homogeneous zone (H) separates the primary dentine (P) from the secondary dentine (S), in the part of the lesion where the odontoblasts had died, or shed their fibrils; whereas the primary and so-called secondary tubules are continuous where the adjoining odontoblasts were merely stimulated to renewed dentine formation (R).

It has sometimes happened that when a cavity has been cut, all the odontoblasts have been fatally injured. Fig. 16 shows such a case sixty-five hours after operation. Nevertheless, despite the short duration of the experiment, the deposit of calcific scar tissue was completed, although the odontoblasts had already entirely disappeared. No new hard tissue cells had arrived, and phagocytes had commenced to clear up the debris.

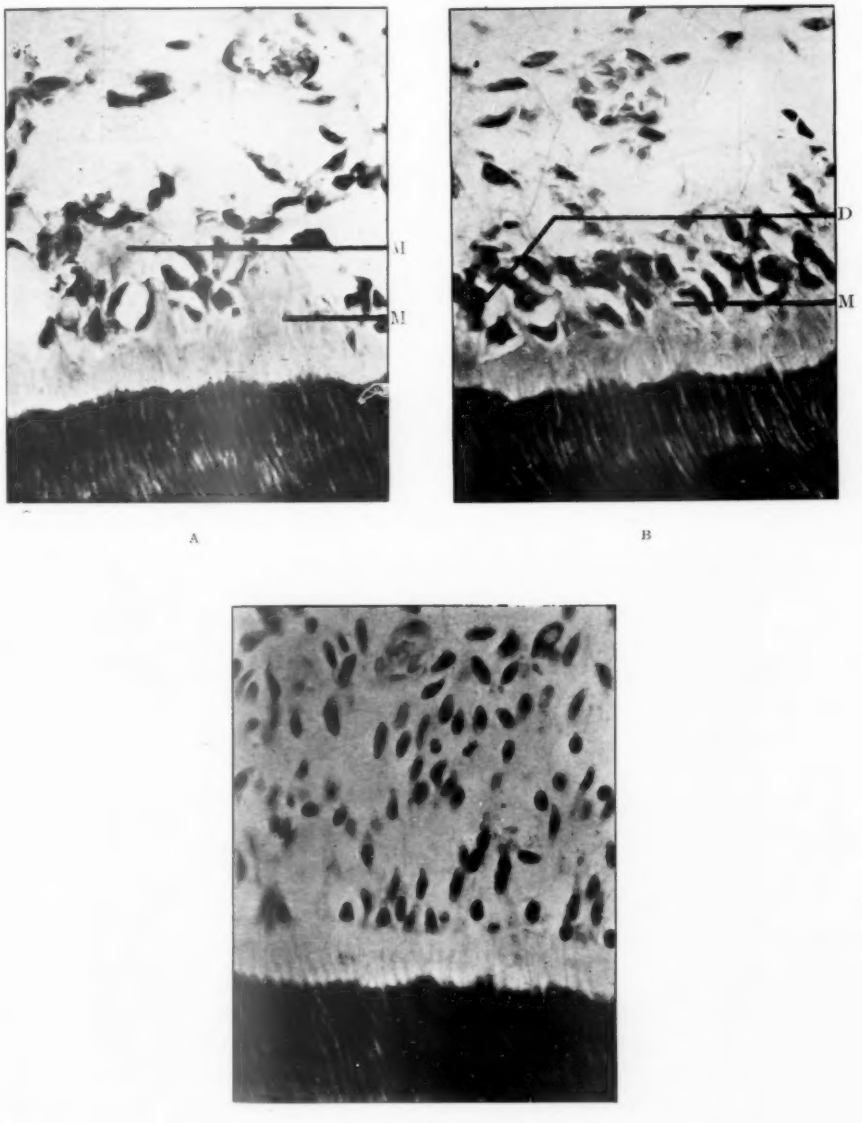

FIG. 15.—A, B, and C.—Photomicrographs × 107 of a decalcified section of the odontoblast layer of a monkey's tooth under an experimental peripheral lesionof the dentine (forty-eight hours) showing early calcific scar tissue (M).

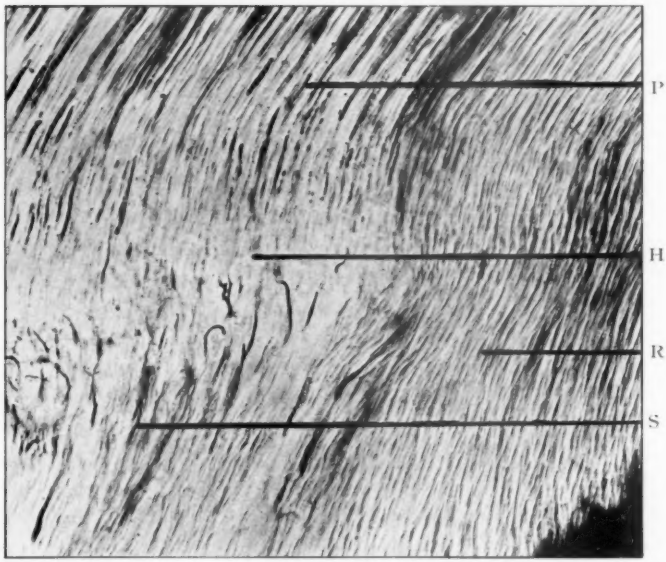

FIG. 15 D.—Photomicrograph × 120 of a ground section of the pulp margin of the dentine of a monkey's tooth under the edge of an experimental peripheral lesion of the dentine (twelve weeks), showing the calcific scar tissue barrier (H); separating the secondary dentine (S) from the dead primary dentine (P), and a recent addition to the primary dentine (R).

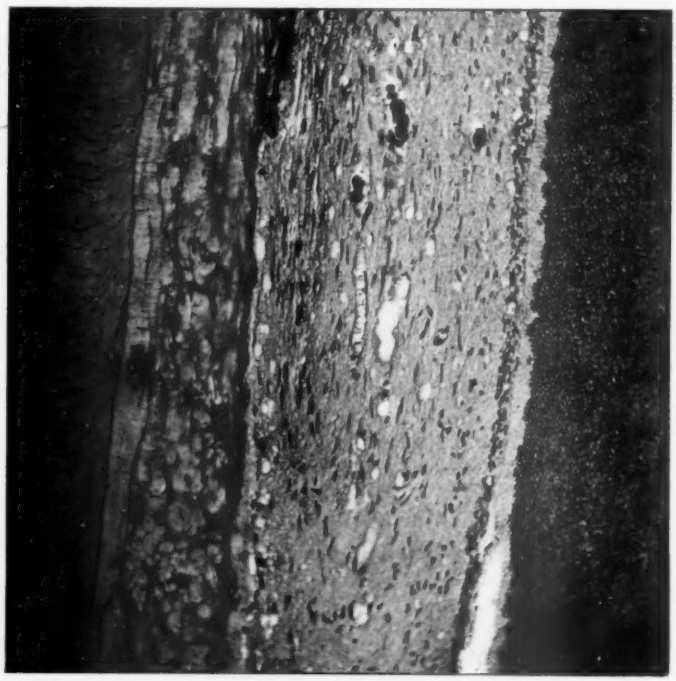

FIG. 17.—Photomicrograph × 185 of a decalcified section of a human molar root showing calcific scar tissue replacing the odontoblasts on one side.

These reactions in their more general application have been fully discussed (Fish, 1931 and 1932), but the rapidity with which this deposit forms and the fact that it forms most quickly round the cells which are most damaged, less rapidly round those which, though damaged, will survive, and not at all round the normal healthy cells, is the significant observation for the present purpose.

It frequently happens that in later life all the odontoblasts degenerate and disappear from the pulp in the roots of human teeth, especially molars. In such cases the disintegrated cells are replaced by a homogeneous layer of calcific scar tissue which is generally called laminated secondary dentine. This layer is wider than would have been the case if the cells had suddenly disintegrated, suggesting that odontoblast degeneration in human teeth is a slow process. In fig. 17 degeneration has taken place, as commonly occurs, on one side of the pulp and not on the other.

A similar reaction can be produced experimentally. A monkey was anæsthetized and a lower incisor tooth was extracted after cauterizing the gum margin to prevent infecting the pulp and root. The apical half of the root was cut off with a sterile saw and implanted into the medullary cavity of the femur, through a window cut out of the cortical bone.

Twenty-one days later the animal was killed and the tooth root sectioned in situ. Its outer surface was absorbed in places by osteoclasts derived from the femur, and calcific repair tissue was deposited round it by cells having the same origin. Inside the tooth, the odontoblast layer had completely broken up and the pulp resembled adult fibrous tissue. It had not been invaded by any new cells but nevertheless the whole pulp chamber was lined with a narrow layer of calcific scar tissue replacing the odontoblasts which had died, here and there the new matrix encloses the few degenerated and disintegrating odontoblasts which remained (fig. 18). This deposit is uniform in thickness all round and corresponds in amount to the quantity which is seen to form when the whole layer of cells degenerates under a peripheral injury to the dentine.

The result was the same when the tooth was implanted into muscle, and there was then even less danger of other mesenchyme cells interfering in the experiment. This reaction occurred in greater or less degree in 10 out of 17 implants ; in one of the others the pulp survived unaltered, and in two the pulp was invaded by phagocytes ; two were infected and the other two could not be found again. Certainly one of these last two had been absorbed.

Exactly the same result was observed when multi-rooted teeth in monkeys were cut across by means of a dental bur so that one root was severed from the tooth below the line of gum attachment. Both tooth and root were left in situ and the small wound was closed. After five weeks there was a deposit of calcific scar tissue in the pulp chamber exactly like that in fig. 18. Another way in which this result was also produced was by destroying the apical vessels of one root of a multirooted tooth.

A corresponding phenomenon takes place normally at the senile end of the pulp chamber in a guinea-pig's tooth (Fish and Harris, 1934). The life-history of the odontoblast in a guinea-pig molar is known to be complete in about twenty-five days. During the last three days in the life of the pulp a considerable mass of calcified collagenous matrix is formed amongst the disintegrating odontoblasts and seals up the pulp chamber ; indeed, most of this calcific scar tissue forms on the last day.

Fig. 19 shows the type of cells amongst which it is being deposited. In twenty-four hours the part of the pulp chamber shown in the lower half of fig. 19 would have moved up with the tooth as it is erupted and at the same time would have become filled with the kind of irregular scar tissue seen already in the upper half.

A few odontoblasts from lower down in the same tooth are inset for comparison, and it may be seen that no normal cell appears to take part in the production of this calcific scar tissue. Just as in the implanted tooth of the monkey, this mass of

calcific scar tissue in the guinea-pig's tooth seems to be formed by cells which are rapidly approaching dissolution. The new calcific deposit does not display the pattern which odontoblasts would leave in the matrix if they were in health, nor has it the pattern which any other known hard tissue cell would leave, such as that of the calcific repair tissue already described.

IV.—Composite Deposits

In a series of experiments following up the earlier investigation of the effect of scurvy on the pulps of persistently growing teeth (Fish and Harris, 1934) it has been found that, when the animal is cured of scurvy, the deposit of calcific scar tissue begins to form within forty-eight hours of restoring the vitamin to the diet, and that it continues to form amongst the degenerated odontoblasts despite the fact that these cells do not recover. As soon, however, as normal cell growth has become re-established in the general tissues of the animal, the embryonic mesenchyme cells of the dental papilla deposit a layer of calcific repair tissue over the mass of calcific scar tissue. A similar result is obtained if the pulp has been injured surgically. The calcific scar tissue formed amongst the injured and dying odontoblasts is covered over with calcific repair tissue by the rapidly proliferating cells of the dental papilla.

In a further series of experiments a hole was drilled through the incisors of rabbits and guinea-pigs halfway up the pulp-canal completely disorganizing the pulp at the site of injury. The results always followed the same course; calcific scar tissue formed around and amongst the injured odontoblasts and calcific repair tissue was deposited over it by young mesenchyme cells which poured into the breach as soon as they recovered. If the injury was exceptionally severe or sepsis supervened, osteoclasts made their appearance at a well-marked distance from the infected zone, and the calcific repair tissue was formed further away still.

Sterile dentine chips were either incorporated in the calcific scar tissue or surrounded by primitive and highly irregular calcific repair tissue depending on whether they lay amongst dying odontoblasts or active young mesenchyme cells. The whole reaction seemed rather a waste of effort in a persistently growing tooth at a point which was so very near to eruption, but is perhaps an example of the marked autonomy of these cells whose activities are controlled only by the change in their environment and their habitual reaction to given stimuli.

When the growing end of a rabbit's molar (M, fig. 20) was injured surgically by scraping it with a probe, both active odontoblasts and undifferentiated mesenchyme cells were involved. A composite mass of calcific scar tissue and calcific repair tissue was therefore laid down. In this case fourteen days had elapsed between the operation and the animal being killed.

In one place (O), the mass of calcific scar tissue (C.S.T.) is being absorbed; at another (C.R.T.) calcific repair tissue is being added to it. At a third point (D) even dentine is being added by odontoblasts which have escaped injury or have differentiated since from the persistent dental papilla.

Such composite experimental masses, curiously resembling odontomes, illustrate the close similarity if not actual identity which exists between the intercellular matrix of bone, dentine, and calcified tissue of repair, since the appropriate cells have drawn the characteristic pattern of each in different parts of this one specimen of matrix.

Discussion

In considering the tissue described as calcific scar tissue it is necessary to give due weight to the essential fact that this calcified collagenous matrix is formed amongst cells which are not healthy. In earlier experiments where it was seen to form under peripheral injuries to the dentine amongst the odontoblasts which had been injured, it was supposed that it represented the first attempt of these cells, after their recovery, to resume their normal labours.

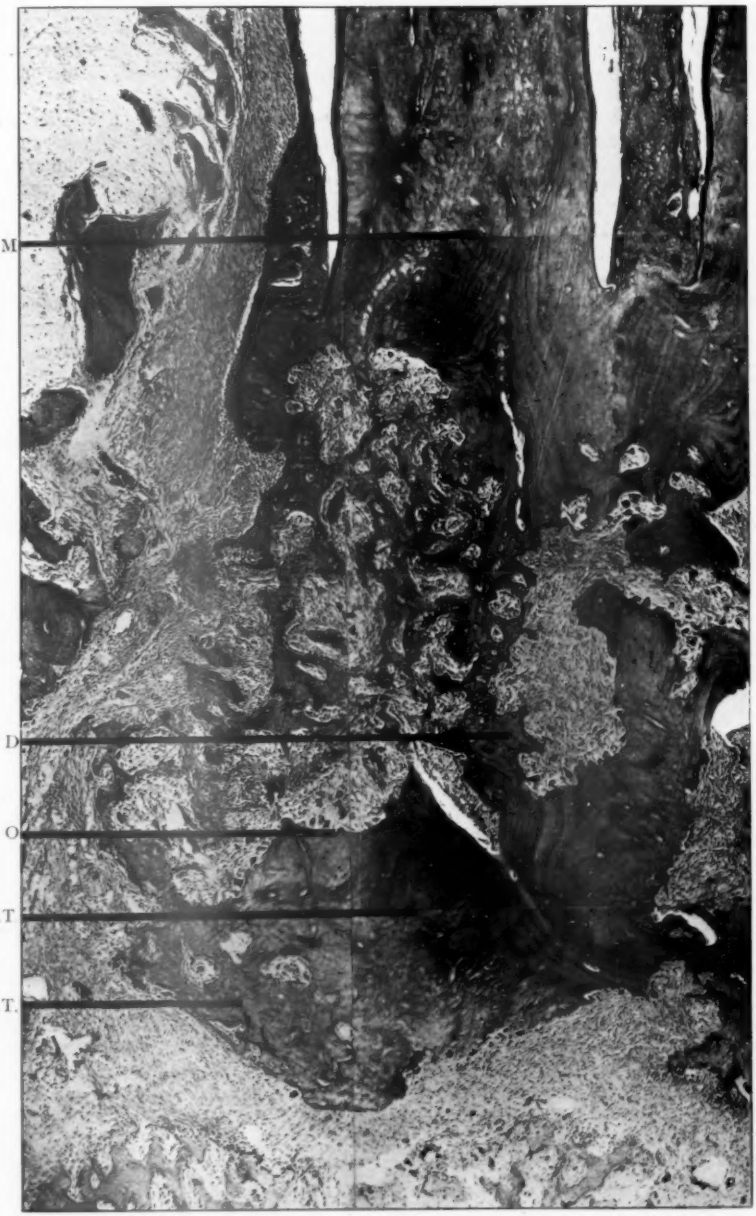

FIG. 20.—Photomicrograph × 48 of a decalcified section of a rabbit's tooth (M) showing a composite mass of calcified tissue of repair consisting of calcific scar tissue (C.S.T.) and calcific repair tissue (C.R.T.) (fourteen days).

It was found, however (figs. 15 and 16), that it actually began to form before the cells had recovered, and later this observation was confirmed, for in implanted teeth (fig. 18) it was formed amongst cells which never did recover but were disintegrating and dying, if not already dead at the time.

These observations, coupled with the similar conditions observed in persistently growing teeth, suggest the possibility that an enzyme is shed from the disintegrating cells which acts upon the tissue fluid and brings about the deposition of collagen in much the same way as phosphatase determines the deposition of calcium salts or perhaps more accurately in the way that thrombokinase starts the reaction which leads to the deposition of fibrin. It was observed that deposition was prevented if the tissue was overheated by the grinding, or invaded by sepsis, or if the animal suffered from scurvy; in fact, if any circumstance interfered with the free movement of normal tissue fluid round the disintegrating cells.

An enzyme reaction for the production of the organic as well as of the inorganic fraction of the calcified collagenous matrix by the cells would, moreover, conveniently account for the translucent zone of Tomes, for the damaged fibril might by analogy be expected to discharge the necessary enzymes into the tissue fluid space of the tubule and bring down a deposit of collagen which in due course would calcify.

The importance of determining the mechanism by which calcific scar tissue is produced lies in the fact that it has a very significant bearing on the biological status and origin of the calcified collagenous matrix in general, for apparently the actual matrix is in all essentials identical in bone, dentine, and cementum, and in these calcified tissues of repair.

In the recent state, for instance, it is in each case impermeable to ordinary dyes (Jeffery, 1932, and Fish, 1931 and 1938). When decalcified, the staining reactions of the organic residue are the same in all of them. The quantitative as well as the qualitative chemical composition approximates very closely, if allowance be made for the extra cell content of bone. X-ray crystallographic examination shows the inorganic content of each to be calcium apatite (Thewlis, 1932) and treatment of the organic part with the usual fluorescent solutions gives the same colour under he ultra-violet microscope.[1] Deposition of calcium salts in each is affected by lack of vitamin D (Mellanby, 1927); similarly deposition of the collagenous organic part of the matrix is disturbed in all of them by deprivation of vitamin C (Fish and Harris, 1934).

If, however, the matrix be regarded simply as the product of enzymes secreted by the cells into the tissue fluid it cannot be expected to exhibit any of the phenomena normally associated with living tissue, and indeed if the cell be regarded as the fundamental unit of life an extracellular, continuous deposit such as bone matrix cannot be regarded as alive.

Without risking a metaphysical argument of that nature it may be pointed out that not only is the fully calcified matrix highly impermeable, but that despite all the irritation to which it was subjected in these experiments it has never been observed to respond in any way whatever.

If bone is infected the cells in it die (Fish, 1939 (i)) but the matrix remains a derelict sequestrum unabsorbed and essentially unchanged, a convenient refuge for invading parasites. Nearby, where the contamination of the matrix is less severe, it still exhibits no response but is absorbed by osteoclasts; further away still it is buried by osteoblasts under new deposits of matrix. Even these deposits may be absorbed later and replaced by a better designed and more habitable structure.

There is no evidence, even, that any chemical change ever takes place in a fully calcified matrix. In hyperparathyroidism, for instance, calcium is not washed out

[1] An observation for which I am indebted to Dr. Herschdörfer, with whom I have investigated the point.—Author.

of the bones but set free by osteoclasts digesting out the organic matrix. The surface of Howship's lacuna remains as hard as ever and the dentine, which is not attacked by osteoclasts in this condition, maintains its normal calcium content (Fish, 1932). Indeed, throughout the life of the animal the matrix itself appears to be entirely inactive; it is irrigated and drained, destroyed and rebuilt, or even sealed up and abandoned by the cells which live in it and around it.

Another indication of the control which is exercised by the cells over the matrix is afforded by studying the varieties of pattern which they weave into it as it is deposited.

Bone affords perhaps the best example of the way in which the individual cell has evolved and increased in efficiency step by step with the evolution of the animal as a whole. From the acellular bone of the Teleostei or the irregular lacunæ and tortuous canaliculi of primitive amphibia has evolved the perfect geometric pattern of the Haversian systems. This has been worked out by G. N. C. Crawford and is in course of publication. Meanwhile he has kindly lent the ground section of normal

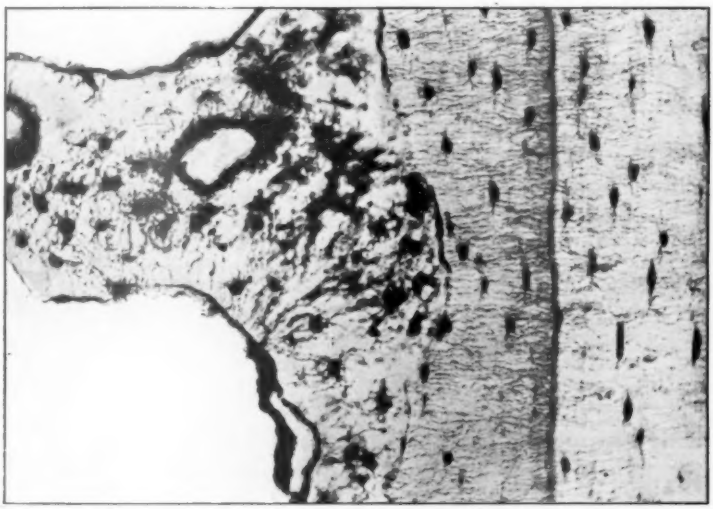

FIG. 21.—Photomicrograph × 280 of a ground section of normal long bone of Iguana (G. N. C. Crawford's section).

reptilian bone from which fig. 21 is taken, and it will be seen that the variety of cell pattern found in these primitive animals bears a striking resemblance to the calcific repair tissue in figs. 6, 11, 12, &c.

It is perhaps reasonable to suppose that under the stress of toxic or mechanical irritation or in the disordered growth of a neoplasm the mesenchyme cells of the mammals should revert to their more primitive habit, and though compelled by their very nature to produce a calcified collagenous matrix, should yet fail to dispose themselves and their processes in the ordered sequence of the Haversian pattern. Such a simple explanation would account for the appearance of calcific repair tissue wherever young undifferentiated mesenchyme cells are irritated.

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SUMMARY

An attempt is made to describe, reproduce experimentally, and classify the numerous types of calcified tissue of repair. Two chief varieties have been observed in both human-pathological material and in experimental animals: these are referred to as :—

(*a*) "*Calcific repair tissue*": Formed when the undifferentiated mesenchyme cells associated with bone dentine or cementum are stimulated into abnormal activity.

(*b*) "*Calcific scar tissue*": Formed when mesenchyme cells which are already *specialized* as odontoblasts are injured and caused to degenerate and disintegrate in the presence of normal tissue fluid.

Both these tissues consist of a calcified collagenous matrix, but the former resembles bone or cementum in that it has lacunæ containing cells, while the latter is acellular and homogeneous, or perhaps contains the debris of the disintegrated odontoblasts.

The cell pattern of calcific repair tissue varies from that of coarse fibre bone to one resembling lacunar cementum; actually, it is identical with that of primitive bone. It is suggested that under the stress of irritation the mesenchyme cells exhibit recessive tendencies and lay down this primitive tissue. The best-known example is callus, but several other varieties are described, which occur in routine dental pathology, and which have also been produced experimentally.

Calcific scar tissue, in contradistinction, forms amongst disintegrating adult odontoblasts which are about to die, and may be deposited even though no normal healthy cells are present. This suggests that the calcified collagenous matrix of which calcific scar tissue is formed may be deposited in the tissue fluid space by enzymes liberated from the dying cells. The various circumstances in which this tissue is observed in nature or is formed experimentally are described.

The significance of these experiments in determining the biological status of the calcified collagenous matrix of bone dentine and cementum is discussed.

Acknowledgments are due to the Medical Research Council for a grant towards the cost of this investigation, and to Sir Edward Meyerstein for his constant support. The author is indebted to Mrs. Hope Simpson and Dr. S. P. MacGregor for the colour drawings, and to numerous colleagues for the gift of pathological material. The technical work of preparing the sections and photomicrographs has been undertaken by Mr. William Pereira, without whose skill and patient work during the last ten years the investigation could never have been carried through.

LEGENDS FOR PLATE

FIG. 16.—Drawing × 733 of a decalcified section of calcific scar tissue formed on the pulp surface of the dentine of a monkey's tooth under an experimental peripheral lesion of the dentine (sixty-five hours).

FIG. 18.—Drawing × 178 of a decalcified section of calcific scar tissue forming on the pulp surface of the dentine of the root of a monkey's tooth after implantation in the same animal's femur.

FIG. 19.—Drawing × 455 of a decalcified section of the senile end of the pulp of a normal guinea-pig's molar, stained with van Gieson and showing calcific scar tissue forming amongst the degenerated odontoblasts.

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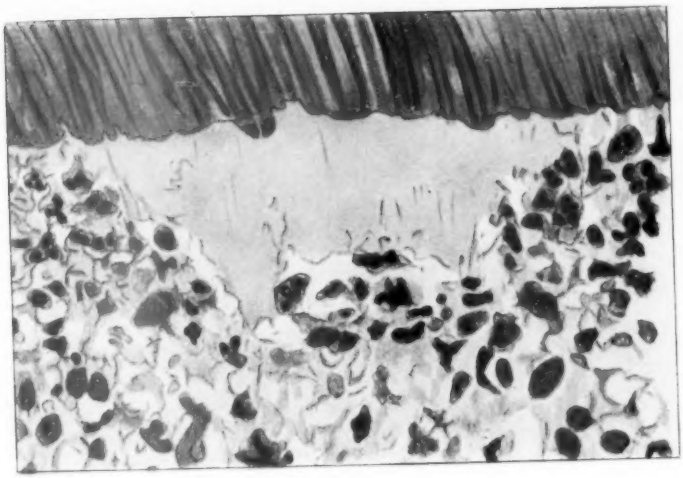

FIG. 16.

FIG. 18.

FIG. 19.

E. WILFRED FISH: Calcified Tissue of Repair.

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The Teeth from a Case of Hypoparathyroidism

By H. F. Humphreys, M.B., Ch.B., M.D.S.

Erdheim in Germany, 1911 [1] and more recently Schour and others in Chicago, 1934–37 [2 and 3] have demonstrated that the removal of the parathyroid in rats produces bands of hypoplasia in these portions of the dentine of the incisor teeth which were calcified subsequent to the operation, but has no effect on dentine already calcified. I have been unable to trace any published human evidence.

Ground Sections were shown from teeth of a woman, D. P., aged 23 (in 1937), whose clinical history can be briefly summarized as follows: She was first admitted to the General Hospital, Birmingham, in 1927, at the age of 12, suffering from fits diagnosed as tetany. Has suffered from intermittent symptoms of tetany ever since. In 1933 noticed that her vision was failing; immature cataract diagnosed 1936. History of acute rheumatism at age of 12 shortly before onset of tetanic symptoms, otherwise nothing of significance in personal or family history. Examination (November 1936) showed serum calcium persistently low (6·5–7·0 mgm. per 100 c.c.), urine calcium, serum phosphorus, and serum phosphatase normal. Examination of stools showed no steatorrhœa, radiographs showed normal structure of bones and no signs of rickets. Daily injections of parathormone improved the symptoms and brought the blood-calcium up to 9·0 mgm. per 100 c.c. Three carious teeth were removed (7.10.37). Ground sections were prepared from the root of 1st molar recording the calcification from 6–9 years, a second lower premolar calcified 4–14 years, and a second lower molar calcified from 4–15 years. The sections supported one another in showing some hypoplasia of enamel dating from before the age of 6 years (this was evident in the permanent incisors also), but no evidence of disturbance in the calcification of dentine before the 9th year. Dentine calcified subsequently, and especially after 12 years, shows changes resembling very strongly those from parathyroidectomized rats with a long survival period after operation. The chief characteristics were (*a*) a great exaggeration of the incremental or contour lines normally seen. Bands of fairly normal dentine alternate with bands, showing coarsely granular matrix with interglobular spaces. (*b*) Parathyroprivic rats show vascular inclusions in the newest formed layers of dentine. The corresponding human dentine also shows blood-vessels surrounded by calcified tissue at the pulp margin, but the appearance is less regular than in rats and resembles osteodentine or bone.

That these appearances, either in the rats or in the human, are not necessarily specific to lack of parathormone but probably represent a general reaction to any agent causing a disturbance in the normal process of calcification is shown by a section taken at random from the incisor of a wild rat which shows similar appearances. The case of D. P. taken in conjunction with the experimental evidence from rats and from work in other fields suggest certain conclusions which must be regarded as tentative only, important as they are.

We do not fully understand the process of calcification of tissues, but it would appear that in the non-vascular dental tissues it differs radically from the process in

bone. In the latter we know calcium metabolism to be active throughout life. Deficiency or excess of the vitamins and hormones that regulate calcification can withdraw calcium from fully formed bone or add calcium to it. There is no satisfactory evidence that the same is true of dental tissues (*see* Fish (iv)). Interference with important factors in calcification appears to manifest itself only in tissues where calcification is still incomplete and those fully formed appear to be unaffected; if well formed they are not damaged, if ill formed they are not repaired. This conclusion, if true, must bear on our conceptions of the vitality and metabolism of the calcified portions of the dental tissues, and their reaction to disease and to therapeutic agents.

The case also illustrates the value of the forming dentine as a sensitive register of biochemical change. It gives a permanent record like the revolving drum of the physiological laboratory of alterations, temporary or permanent, in the factors regulating calcification. It is hoped that an examination of the 3rd molar of this case may be possible.

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Section of Orthopædics

President—R. OLLERENSHAW, F.R.C.S.

[*December* 6, 1938]

Injuries to Both Semilunar Cartilages of the Knee-Joint

By C. LAMBRINUDI, F.R.C.S.

THIS is not intended to be an authoritative paper based on a careful study of a large series of cases. It is rather in the nature of an interim report—a kind of feeler to test whether others have had similar experiences to myself, and if so to pool our knowledge in order to arrive at a clear-cut clinical picture.

My first experience with the condition of dual lesion of the semilunar cartilages occurred some five years or more ago while operating on a student at Guy's. He had symptoms of internal derangement of the knee which led me to suspect that the trouble was on the inner side. At the operation I removed a torn anterior half of the internal cartilage and felt satisfied that this was probably the cause of his trouble. By a lucky chance he had one of those rare knees where it was quite easy to look from the inner compartment into the outer, and in doing so I found to my astonishment that the external cartilage was displaced. I regarded this case as an exceptional one, and thought little more about it until recently. During the past two years I have collected eight such cases.

J. T., seen in January 1934 after football injury. At the time felt as if " the whole knee went out " but there was no locking and he continued to play. When I saw him one month later there was a lot of effusion into the joint, he could not get the knee quite straight due, I thought, to spasm. There was marked atrophy of the muscles, and some pain and cystic swelling in the region of the popliteus tendon. I suspected a tear of the external cartilage or strain of the popliteal tendon, and advised him to use the knee normally and do quadriceps exercises. Discomfort in the joint persisted, with pain on the inner side associated with attacks of the knee giving way, and atony of the muscles : so I operated.

On opening the inner side of the joint I could at first detect no abnormality of the internal cartilage, but feeling fairly certain that there was a lesion there I started to remove it, and presently found that it was torn completely across at its middle. I did not remove the posterior half of the internal cartilage but explored the outer side, because when I first saw him I had the impression that the main injury was on that side, and on opening the joint on the outer side I found a posterior bucket handle of the external cartilage, which, seeing that he had had no attacks of locking, must have persisted from the original accident (fig. A, p. 20).

R. J. First seen in May 1937 after gross injury at football to left knee. Felt as if " whole knee went out ". This was followed by large and immediate effusion into the joint and marked pain on the inner side—so much so that he was diagnosed as a strain of the internal lateral ligament and the knee was put in plaster. When I examined him one month later he still had pain on the inner side of the knee, and under an anæsthetic it would not go quite straight. There was no ligamentous laxity. I decided to operate, expecting to find a displaced internal cartilage. Again on opening the joint there was nothing abnormal to be seen, but on proceeding to remove the internal cartilage the anterior half came away without any pull in my dissecting forceps. The knee still would not go quite straight, so I explored the posterior part of the internal cartilage and found that it was quite firmly attached and came away whole. On piecing the two halves together

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By H. F. Humphreys, M.B., Ch.B., M.D.S.

Erdheim in Germany, 1911 [1] and more recently Schour and others in Chicago, 1934–37 [2 and 3] have demonstrated that the removal of the parathyroid in rats produces bands of hypoplasia in those portions of the dentine of the incisor teeth which were calcified subsequent to the operation, but has no effect on dentine already calcified. I have been unable to trace any published human evidence.

Ground Sections were shown from teeth of a woman, D. P., aged 23 (in 1937), whose clinical history can be briefly summarized as follows: She was first admitted to the General Hospital, Birmingham, in 1927, at the age of 12, suffering from fits diagnosed as tetany. Has suffered from intermittent symptoms of tetany ever since. In 1933 noticed that her vision was failing: immature cataract diagnosed 1936. History of acute rheumatism at age of 12 shortly before onset of tetanic symptoms, otherwise nothing of significance in personal or family history. Examination (November 1936) showed serum calcium persistently low (6·5–7·0 mgm. per 100 c.c.), urine calcium, serum phosphorus, and serum phosphatase normal. Examination of stools showed no steatorrhœa, radiographs showed normal structure of bones and no signs of rickets. Daily injections of parathormone improved the symptoms and brought the blood-calcium up to 9·0 mgm. per 100 c.c. Three carious teeth were removed (7.10.37). Ground sections were prepared from the root of 1st molar recording the calcification from 6–9 years, a second lower premolar calcified 4–14 years, and a second lower molar calcified from 4–15 years. The sections supported one another in showing some hypoplasia of enamel dating from before the age of 6 years (this was evident in the permanent incisors also), but no evidence of disturbance in the calcification of dentine before the 9th year. Dentine calcified subsequently, and especially after 12 years, shows changes resembling very strongly those from parathyroidectomized rats with a long survival period after operation. The chief characteristics were (*a*) a great exaggeration of the incremental or contour lines normally seen. Bands of fairly normal dentine alternate with bands, showing coarsely granular matrix with interglobular spaces. (*b*) Parathyroprivic rats show vascular inclusions in the newest formed layers of dentine. The corresponding human dentine also shows blood-vessels surrounded by calcified tissue at the pulp margin, but the appearance is less regular than in rats and resembles osteodentine or bone.

That these appearances, either in the rats or in the human, are not necessarily specific to lack of parathormone but probably represent a general reaction to any agent causing a disturbance in the normal process of calcification is shown by a section taken at random from the incisor of a wild rat which shows similar appearances. The case of D. P. taken in conjunction with the experimental evidence from rats and from work in other fields suggest certain conclusions which must be regarded as tentative only, important as they are.

We do not fully understand the process of calcification of tissues, but it would appear that in the non-vascular dental tissues it differs radically from the process in

bone. In the latter we know calcium metabolism to be active throughout life. Deficiency or excess of the vitamins and hormones that regulate calcification can withdraw calcium from fully formed bone or add calcium to it. There is no satisfactory evidence that the same is true of dental tissues (*see* Fish (iv)). Interference with important factors in calcification appears to manifest itself only in tissues where calcification is still incomplete and those fully formed appear to be unaffected; if well formed they are not damaged, if ill formed they are not repaired. This conclusion, if true, must bear on our conceptions of the vitality and metabolism of the calcified portions of the dental tissues, and their reaction to disease and to therapeutic agents.

The case also illustrates the value of the forming dentine as a sensitive register of biochemical change. It gives a permanent record like the revolving drum of the physiological laboratory of alterations, temporary or permanent, in the factors regulating calcification. It is hoped that an examination of the 3rd molar of this case may be possible.

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Section of Orthopædics

President—R. Ollerenshaw, F.R.C.S.

(*December* 6, 1938)

Injuries to Both Semilunar Cartilages of the Knee-Joint

By C. Lambrinudi, F.R.C.S.

This is not intended to be an authoritative paper based on a careful study of a large series of cases. It is rather in the nature of an interim report—a kind of feeler to test whether others have had similar experiences to myself, and if so to pool our knowledge in order to arrive at a clear-cut clinical picture.

My first experience with the condition of dual lesion of the semilunar cartilages occurred some five years or more ago while operating on a student at Guy's. He had symptoms of internal derangement of the knee which led me to suspect that the trouble was on the inner side. At the operation I removed a torn anterior half of the internal cartilage and felt satisfied that this was probably the cause of his trouble. By a lucky chance he had one of those rare knees where it was quite easy to look from the inner compartment into the outer, and in doing so I found to my astonishment that the external cartilage was displaced. I regarded this case as an exceptional one, and thought little more about it until recently. During the past two years I have collected eight such cases.

J. T., seen in January 1934 after football injury. At the time felt as if "the whole knee went out" but there was no locking and he continued to play. When I saw him one month later there was a lot of effusion into the joint, he could not get the knee quite straight due, I thought, to spasm. There was marked atrophy of the muscles, and some pain and cystic swelling in the region of the popliteus tendon. I suspected a tear of the external cartilage or strain of the popliteal tendon, and advised him to use the knee normally and do quadriceps exercises. Discomfort in the joint persisted, with pain on the inner side associated with attacks of the knee giving way, and atony of the muscles; so I operated.

On opening the inner side of the joint I could at first detect no abnormality of the internal cartilage, but feeling fairly certain that there was a lesion there I started to remove it, and presently found that it was torn completely across at its middle. I did not remove the posterior half of the internal cartilage but explored the outer side, because when I first saw him I had the impression that the main injury was on that side, and on opening the joint on the outer side I found a posterior bucket handle of the external cartilage, which, seeing that he had had no attacks of locking, must have persisted from the original accident (fig. A, p. 29).

R. J. First seen in May 1937 after gross injury at football to left knee. Felt as if "whole knee went out". This was followed by large and immediate effusion into the joint and marked pain on the inner side—so much so that he was diagnosed as a strain of the internal lateral ligament and the knee was put in plaster. When I examined him one month later he still had pain on the inner side of the knee, and under an anæsthetic it would not go quite straight. There was no ligamentous laxity. I decided to operate, expecting to find a displaced internal cartilage. Again on opening the joint there was nothing abnormal to be seen, but on proceeding to remove the internal cartilage the anterior half came away without any pull in my dissecting forceps. The knee still would not go quite straight, so I explored the posterior part of the internal cartilage and found that it was quite firmly attached and came away whole. On piecing the two halves together

the line of tear could be seen. The knee still would not go straight, so I then explored the outer side and found a posterior bucket handle of the external cartilage.

On reading the account of the first case it might possibly be argued that the lesion I found in the internal cartilage may have occurred after the original trauma, but in this case there can be no possible doubt that the dual lesion was part of the same mechanism, whatever that may be. This man was a very valuable county footballer, particularly renowned for his long-distance kicking, and I had the gratification eight months later of seeing him play as well as ever.

L. G. Twisted his knee at football in 1937. Felt something " go out " and the knee locked, but when the leg was pulled on it went in with a click and he was able to continue playing. When I saw him six months later this same thing had happened six times, and on the last occasion he could not get it back. He complained chiefly of loss of confidence in the knee. Pain was never very marked, but the little he had was on the inner side in the region of the internal lateral ligament. He could not get the knee quite straight, but under an anaesthetic extension was full and there was no suspicion of a click or locking, neither was there any ligamentous laxity. Again I explored the inner side chiefly on account of repeated attacks of locking and some pain on that side. Once more on opening the joint all appeared to be normal, but on proceeding to remove the internal cartilage the anterior half came away in my dissecting forceps. It was obvious this could not account for his recurrent attacks of locking, so I explored the outer side and found a posterior bucket handle of the external cartilage. I did not explore the posterior part of the internal cartilage.

D. M. First seen in March 1938. Twisted knee taking backhand at tennis and felt something click. She could not localize the click, but on account of the discomfort went to an osteopath who " put the cartilage in ". Two weeks later the same thing happened again, and since then the knee has never felt safe and gave a sensation of " wobbling ". On examination there was no ligamentous laxity, no limitation of movement, but I could detect a slight click on the inner side and what little pain she had was on the inner side in the region of the internal lateral ligament. I explored the internal cartilage and again everything seemed to be normal, but on dissecting it along the periphery the anterior half came away in my forceps. Not feeling satisfied that this was the cause of her trouble I explored the posterior half of the internal cartilage and found that there was a detached tag (fig. B). I removed the whole cartilage.

In view of the similarity of this lesion with the other three cases I felt very much inclined to explore the outer side but I refrained from doing so hoping that the posterior tag might account for her symptoms. Two months ago she returned complaining of exactly the same feeling of the whole knee wobbling. She had had two such attacks and there is not the slightest doubt that her symptoms are now on the outer side. I hope shortly to have an opportunity of exploring the knee again.

This is a particularly significant case because at operation I suspected the external cartilage, not because of her symptoms, but because of the nature of the lesion in the internal cartilage.

P. J. First seen in April 1937. One year previously she fell and twisted her knee while catching a girl vaulting. She had a great deal of pain in the whole knee, most marked on the inner side, and there was immediate and large effusion. Her doctor thought she had strained the internal lateral ligament and treated her for it. The knee never got comfortable after this, and one month previous to my seeing her she felt " the whole knee slipping in and out " while playing lacrosse. The same thing happened again one week before I saw her. On examination extension was full, there was no clicking, she had some pain on the inner side in the region of the internal lateral ligament, there was definite ligamentous laxity, and atrophy of the muscles. I manipulated her under an anaesthetic and broke down some adhesions, but could feel nothing suggestive of a loose cartilage. In May, while playing tennis, she felt " something in the knee click in and out " and there was pain on the inner side, so I decided to explore the joint. On this occasion because of the vagueness of her symptoms, I explored the outer side first and found that the posterior part of the external cartilage had been ruptured; it was flattened and discoloured from an old haemorrhage. Out of curiosity and because she had so frequently referred her pain to the inner side I then explored the inner side and found a transverse tear exactly as in the other cases. She continued very well for a time, but in December 1937 she again had several attacks of " the whole knee going out unaccountably ". She still had atrophy of the muscles and ligamentous

laxity, and on examination I felt a click on the inner side so I decided to explore the posterior part of the internal cartilage and I found a longitudinal tear in it with a tag as per fig. B. The knee was very wobbly under an anæsthetic, so I made a complete exposure by reflecting the patella, and found that the anterior crucial ligament was torn and frayed. I made no effort to repair it. She now writes and tells me that her knee feels much stronger and she is able to resume her post as gymnastic mistress, and on only one occasion this term has she had that feeling of the knee going out.

H. About three years ago she twisted her knee playing tennis. She had immediate and large effusion and great pain in the knee. This pain was most marked on the inner side. There was some lateral wobble, and at that time she was seen by an orthopædic surgeon who diagnosed strain of the internal lateral ligament and put the leg in plaster. The knee never felt strong after this and she had attacks of " the whole knee going out " with pain on the inner side. She was seen by another orthopædic surgeon about one year later who operated on the inner side and who (as I found by a later operation) must have only removed the anterior half of the internal cartilage. Her symptoms, however, persisted, and she described it as the " whole knee going out unaccountably, accompanied by a crunching feeling ", and when I examined her there was marked ligamentous laxity, atony of the muscles, and under the anæsthetic I felt a definite click in the external cartilage. At operation I explored the posterior half of the internal cartilage and found it intact apart from a small tag as in the previous cases. The whole of the posterior half came away as a separate piece, and there was no doubt at all that the anterior half had been removed previously. I then explored the outer side and found that the external cartilage, though not displaced, was extremely movable. The posterior part came forward with the slightest pull, and I was able to remove the cartilage complete. Since the operation, now four months ago, she has only had two attacks of the knee letting her down, and on both occasions there was a definite cause, such as slipping over a rug. She is able to hike, dance, and run quite comfortably, but she does not feel secure when side-stepping. Previous to the operation the attacks were very much more frequent and occurred unaccountably, so I think again I can claim that in spite of the fact that the ligamentous laxity persists the removal of both semilunar cartilages has in some way ameliorated her symptoms.

B. E. This case is not yet proven because he refuses to submit to a further operation, but I think that clinically he undoubtedly belongs to this group. Ten years ago he fell playing tennis and strained the knee. Two years later, owing to recurrent attacks of effusion and the knee giving way, a general surgeon removed the internal semilunar cartilage which he stated was torn. The symptoms of which the patient now complains are exactly similar to those which he had before operation, namely, insecurity and attacks of the" knee letting him down accompanied by a wrenching feeling ". He has been treated for a long time by an orthopædic surgeon for quadriceps insufficiency, and was sent to me for a second opinion. When I saw him he had appreciable ligamentous laxity, marked atony of the muscles, and a definite click on the outer side. Clinically I had no doubt that he had a loose external cartilage and advised him to have it removed, but he refused, and later he was advised to wear a knee-cage, with which he is very contented.

There was some correspondence between another orthopædic surgeon and myself with regard to the last case.

I. P. I saw him in December 1937. He had twisted his knee skiing and felt immediate and great pain in the whole joint, but when I saw him he had no definitely localized pain. Two months after the original accident he had another attack and felt something slipping in the knee but had no locking. This occurred 15 times. He was seen by an orthopædic surgeon who attributed his attacks to ligamentous laxity and ordered him a knee-cage. When I saw him he had given this up as it was too cumbersome, and his chief complaint was insecurity and attacks of the whole knee giving way, accompanied by a churning, crunching feeling in the joint.

On examination there was a sensation on the outer side of something catching, and I came to the conclusion that it was a loose external cartilage. I wrote to Mr. A., the orthopædic surgeon who had seen him previously, and said that I did not think the laxity of the ligaments alone could account for his disability. *By this time I had become suspicious of the external cartilage when patients had to invent words to express their subjective sensations.* He described his feelings as " crunching and churning ", others of " the whole knee going out ", another of " the whole knee

wobbling ", and again another of " attacks of wrenching ". A patient with an ordinary internal cartilage very rarely has difficulty in expressing himself. As I thought that the sensations he described were more likely to be due to an external semilunar cartilage I advised Mr. A. to explore that cartilage and at the same time to examine the inner one since I had come across several cases of dual lesions. He answered :—

" I operated on young I. P. yesterday. There seemed to be a good deal of stretching of the posterior ligament on the side which I demonstrated to the parents before I operated. At the operation I found that, as you thought, he had a lesion of the internal cartilage. There had been a split about the middle of it and a small piece had separated with a pedicle and the terminal part flattened and I have no doubt this was getting in between the bones on certain movements. I removed the cartilage."

The patient returned to me two months later complaining of precisely the same " crunching churning " feeling, and I wrote to Mr. A. again and advised him once more to explore the outer cartilage and described in detail some of my own cases. He replied in April after having performed the second operation, as follows :—

" I operated on I. P. this morning and removed his external cartilage. It was split in the posterior horn so I am hoping that everything will be all right now. There were a good many fatty tags in front which I also removed."

I examined this patient again yesterday and he tells me that his knee feels perfectly safe and he can do anything he likes. The tone of the muscles is absolutely perfect, but some degree of ligamentous laxity persists. The only time he gets a reminder that the knee is not quite normal is on sudden side-stepping and swimming.

This is independent corroboration of the dual lesion that I am attempting to describe, and it is largely due to the interest of Mr. A. that I have been persuaded to read this paper.

From a survey of this small series of cases three things appear to be of outstanding importance :—

(1) In six out of the eight there was pain on the inner side.

(2) In four out of the eight the disability was attributed to quadriceps insufficiency and treated as such for a long time.

(3) In the four out of the eight who had laxity of the ligaments three of them obtained relief of their major symptoms by having the external cartilage removed.

(1) With regard to pain on the inner side it is interesting to note that the majority of my cases had it. This is particularly interesting because the statement is often made that the pain due to a lesion of the external semilunar cartilage is often referred to the inner side. I want to make the suggestion that it is not a true referred pain and that where it exists there is actually a lesion of the internal cartilage as well. It is probably true to say that this lesion of the internal cartilage is not of the kind that is likely to give rise to mechanical trouble such as locking. It can even be said that on innumerable occasions the external cartilage alone has been removed and no further trouble has occurred, but the practical importance of my suggestion is that on account of pain on the inner side the surgeon may be tempted to explore the inner cartilage first and, finding something definitely abnormal, may be lulled into the belief that it is the cause of the trouble and not think it necessary to explore the outer side. This has happened to four of these cases.

(2) With regard to quadriceps insufficiency, this as a diagnosis, seems to give rise to confusion of thought. When one thinks of the number of cases of, say, old infantile paralysis where the bulk of the quadriceps muscles is considerably reduced yet the patient complains of no disability one must, I think, begin to doubt it. I am quite convinced that the loss of voluntary power as represented by a wasting of 1 in., 1½ in., or even more is not the cause of insecurity. We all realize that for the protective reflex mechanism of a joint the thing that matters is tone rather than power—of course within limits. In this connexion I was particularly interested in a remark made by Sir Herbert Barker at his demonstration at St. Thomas's Hospital a little

time ago. He said that you could always detect if a cartilage is out of place by the shape of the thigh, and that the contour alters as soon as it is replaced. I believe this is a fundamental observation, and in reality he was alluding to the tone of the muscles. The symptoms associated with the diagnosis of so-called quadriceps insufficiency are a sense of weakness and attacks of letting one down. I imagine that convalescence must give one a very good idea of what one has in mind when talking of quadriceps insufficiency, but in that state I can vouch for it from my own experience that the weakness of my knees bore no relationship to voluntary muscular power. I was able to do knee-bending exercises and get up from a chair long before I felt safe on my pins—moreover, in convalescence one stumbles but rarely falls. In this state, of course, one is dealing with a generalized atony which causes a delay in the timing of the protective reflex mechanism of the joints and not to a true weakness. But when one comes to consider atony of a single muscle or group of muscles guarding a joint, the question that arises is what causes this local condition. I believe that any focus within the joint which gives rise to a nociceptive stimulus, be it ever so benign such as a single strand of an adhesion, will cause reflex inhibition of tone of the muscles, and any treatment designed only to increase the voluntary power of the muscles, even if this were possible, would not improve the feeling of insecurity until the nociceptive focus within the joint has been eradicated. This consideration brings me to the third subject I wanted to discuss, namely, ligamentous laxity.

(3) The mechanical symptoms associated with cartilage injuries are either that the patient feels something slipping in and out or gets attacks of locking, or the more alarming feeling of the whole knee going out of joint. In all my cases except two the initial trauma seemed to be of a severe kind. They complained that the whole knee seemed to go out and there was an immediate and large effusion into the joint. As a rule, I think, in the ordinary internal semilunar cartilage injury there is not that same feeling of a major catastrophe, neither is there immediate and large effusion unless the trauma has been sufficient to strain the crucial ligaments as well. The difference between the ordinary bucket handle of the internal cartilage and the posterior bucket handle of the external is very considerable. In the former the thickness of the detached margin is not more than $\frac{1}{16}$ to $\frac{1}{8}$ in. In the latter the whole rim is detached, and that is quite $\frac{1}{4}$ in. or more thick. In other words, there must be a momentary distraction of the tibia from the femur of at least that amount in order to allow the posterior part to slip forward, and I suggest that such injuries are more likely to be associated with strain of the crucial ligaments than the ordinary displacement of the internal cartilage. It is significant that in four out of my eight cases ligamentous laxity was present to a very appreciable degree. Now these patients complained that the knee felt insecure and that periodically the whole knee seemed to go out of joint. These symptoms were regarded by their surgeons as due to the looseness of the joint—two of them were given knee-cages and two of them were treated for a long time with quadriceps exercises in the hope of toning up the muscles. In one case a half-hearted suggestion to repair the crucial ligament was mooted. The external cartilage is normally a mobile structure and the coaptation of the tibia and femur helps to keep it in place. If the ligaments are lax it is easy to conceive that a comparatively normal cartilage may occasionally get nipped and give rise to that catastrophic sensation of the whole knee going out of joint. In fact I believe that the grosser symptoms associated with a moderate degree of ligamentous laxity are in reality due to the external cartilage slipping in and out and it is perfectly good surgery in these cases, despite the laxity, to excise the external cartilage even though on exploration it may not appear at the time to be displaced.

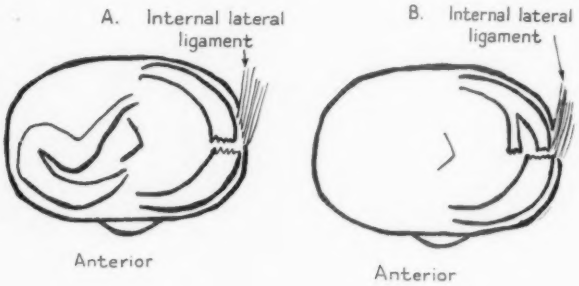
In conclusion I would like to summarize my points in order to facilitate discussion.

(1) Dual lesion of the semilunar cartilages probably occurs more frequently than is realized, and ought to be suspected in all cases where the pain, associated with an injury to the external cartilage, is alleged to be referred to the inner side.

(2) That dislocation of the external cartilage is more likely to be associated with strain of the crucial ligaments than is the case with internal cartilages.

(3) That the diagnosis of quadriceps insufficiency should be abolished as it gives rise to confusion of thought.

(4) That the alarming symptoms associated with moderate degrees of ligamentous laxity are in reality due more to the slipping in and out of the external cartilage than to laxity itself, and that in these circumstances excising this cartilage is a sound procedure.



Name	Nature of accident	Time of effusion into joint	Mechanical effect	Quadriceps muscle	Ligamentous laxity	Pain on inner side
J. T.	Twist at football	Same evening	No locking, extension full, whole knee seemed to go out of joint	Marked atony	Nil	Yes
R. J.	Twist at football	Immediate and large	Felt as if whole knee went out. Extension limited	Wasted	Nil	Definite. Treated as strain of inter. lat. lig.
L. G.	Twist at football	Same evening	Locking. Went back with a click. This occurred 6 times, and the last time he could not extend the knee	Marked atony	Nil	Yes. No pain on outer side
D. M.	Slipped while taking back-hand shot at tennis	Slight	Something clicked. Later at another attack felt as if knee wobbled	Slight atony	Nil	Yes, click on inner side felt on examination
P. J.	Twisted knee when catching girl vaulting	Immediate and large	Felt as if whole knee went out. No locking, able to get knee straight. Later felt something go in and out	Marked atony	Definite laxity	Marked on inner side. Thought to be strain of internal lateral ligament
H.	Twisted knee playing tennis	Immediate	Felt as if whole knee goes out	Marked atony	Marked	Marked on inner side. Treated as torn internal lateral ligament
B. E.	Twisted knee playing tennis	?	Felt insecure and had attacks of wrenching	Atony	Marked	Nil
I. P.	Twisted knee skiing	Immediate	Felt something slipping in and out. Later felt as if knee goes out of place. Described as "churning feeling"	Atony	Marked	No localized pain

6 out of 8 had pain on inner side.
5 out of 8 were treated for a long time for quadriceps insufficiency.
4 out of 8 had marked ligamentous laxity.
4 out of 8 had large and immediate effusion into the knee-joint.

Congenital Coxa Vara and the Short Femur

By CAMPBELL GOLDING, M.R.C.P., Ch.M., D.M.R.E.

ALTHOUGH this is a subject of relatively small importance, much time might be devoted to a historical survey of the condition which has been variously described as infantile, cervical and congenital coxa vara. Only those few contributions to the literature are considered which have some bearing on the type of radiograms which will illustrate this paper.

In the early nineteenth century, the types of coxa vara were confused, and it is difficult to separate the various conditions in the published descriptions. In 1894 Hofmeister, and in 1896 Kredel, described congenital coxa vara and recognized the frequent association with other congenital deformities.

In 1897 Kirmisson reported two autopsies on infants of 1 and 2½ months with congenital coxa vara, a host of other reports have since appeared illustrating the congenital origin of the conditions.

In 1903 Reiner showed that it may be associated with defective development of the femur. In 1905 Hoffa differentiated the condition from rickets and mentioned the vertical epiphyseal line.

In 1913 Elmslie recognized and described the fragmented neck and the "V"-shaped defect in the neck. In 1927 and 1928 Fairbank reported the post-mortem findings in a case and published a complete description which will be referred to later. This year the President has surveyed the subject in the modern manner with a moving picture. There are also in the literature the findings of nine surgeons who have operated on one or more patients, with a description of sections removed at the operation. Nothing has been gained from these sections which could not have been inferred from the radiograms; they have not contributed any special information towards the ætiology.

I propose to place in the same group infantile and congenital coxa vara and to include the micromelia due to the short femur. The latter appears to be merely a variation of, and in some patients, the early stage of the same condition.

The radiographic features of congenital coxa vara are tabulated below, not all of them are present in each patient.

(1) An oblique or vertical defect in the neck.

(2) A varoid deformity.

(3) A short neck.

(4) A fragmented neck.

(5) Incomplete ossification in part of the neck.

(6) Beaking of the great trochanter.

(7) A facet formed by this trochanter on the ilium.

(8) Secondary deformity of the acetabulum due to the malposed head.

At the Royal National Orthopædic Hospital, radiograms have been kept since 1912, and one is able to trace the complete development of the abnormality in a few patients.

The stages of development may also be shown by a series of radiograms of different patients commencing with the minimum deformity and working backwards to gross

FIG. 1.—The minimum deformity of congenital coxa vara without fragmentation of the neck.

FIG. 2.—The same patient as fig. 1 at an earlier stage. This type with a triangular fragment in the neck, is frequently termed infantile coxa vara, but the separation of these two conditions would hardly appear to be justified. (Patient of Mr. Seddon.)

FIG. 3.—A very short neck, with an area of increased density on the inner part of the shaft which is also illustrated in later films.

FIG. 4.—Showing the presence of two triangular fragments.

maldevelopment of the femoral neck. The minimum deformity necessary to establish a diagnosis consists of an oblique or vertical epiphyseal line and a varoid neck which may be quite well developed, that is without a " V "-shaped fragment or other evidence of aplasia. These are presumably patients who began with an imperfectly ossified neck which ultimately developed normally. My reason for saying this is based on films such as these (*see* figs. 1 and 2).

The next stage in the condition is due to defective ossification in the neck ; this may be apparent as (1) a very short neck (*see* fig. 3), (2) incomplete ossification, especially towards the femoral head (*see* fig. 11). (3) Fragmentation of the neck either in the form of small bony fragments lying in cartilage or a " V "-shaped fragment which may be present at the upper or lower border of the neck (*see* fig. 4). The latter is probably the most frequent type of congenital coxa vara. The next stage of the deformity consists of a varying degree of aplasia of the upper half of the shaft of the femur. The upper half of the femur is short and thin, in the region of the lesser trochanter there is often a second varoid deformity, the cortex at this level on the inner side may be increased in width or replaced to some extend by a translucent zone resembling a fracture, this translucent zone may extend completely across the shaft with marked varus at the site. In other words, the neck is not the only site at which ossification may be incomplete ; this may occur below the trochanters forming a second translucent zone. A peculiar feature is that the upper translucent zone in the neck disappears much earlier than the normal epiphyseal line (*see* figs. 5, 6, 7, and 8).

In this description, the stages of the process have been described in reverse order. There are in this series three patients who have been followed for many years. They illustrate the imperfect progress of the deformity commencing with only the lower half of the femur formed in bone to the development of a malformed shaft and neck. One of these patients formed a comparatively good shaft, but the ossification at the upper end was incomplete and resulted in a congenital coxa vara (*see* figs. 9, 10, 11, and 12).

The triangular fragment in the lower part of the neck is a typical feature of one of the types of this deformity. It is not denied that these fragments exist, but they may be artificially produced, sometimes by normal radiographic technique, and similarly may be made to disappear. In the last film a triangular fragment is visible ; while this patient was still on the X-ray table the leg was rotated and the fragment vanished. It is obvious that it was produced by the anterior and posterior margin of the translucent zone.

Fairbank has said that he does not believe that anteversion of the neck plays an important part in the condition. This was borne out by lateral views of these patients.

The same author has also mentioned that the varus increases with age unless ossification takes place. This is probably the most important single point in the disease. In untreated cases the extent of the deformity depends upon the thickness of the shaft and the rapidity and degree of ossification.

Late stages.—If the neck is imperfectly ossified in later life the upper part is usually more complete than the lower. This strip of bone is easily fractured. In other patients there is complete absence of ossification. When ossification does take place there often remains a difference in texture between the neck and the head, sometimes a trace of the translucent zone is seen as a permanent feature of the disease (*see* figs. 13 and 14).

It is not intended to convey an impression that the only and inevitable termination of the short femur is a condition of congenital coxa vara. There were three patients in this series who began life with a short femur. One of these now (aged 8 years)

FIG. 5.—Note the increased density on the inner part of the shaft and a partial translucent zone at this site.

FIG. 6.—The two translucent zones extend completely across the shaft with marked varus.

FIG. 7.—The late result of a patient similar to fig. 6.

FIG. 8.—The late result when the lower translucent zone does not ossify.

FIG. 9

FIG. 10

FIG. 11

FIG. 12

FIGS. 9, 10, 11, and 12.—Show the complete development of congenital coxa vara in the same patient from 1925 to 1938.

FIG. 13.—A trace of the translucent zone is still present and the head is less dense than the neck and shaft.

FIG. 14.—The typical late result when there has been complete failure of ossification in the neck.

has no deformity beyond a short limb. The others hold the limb in flexion, abduction and external rotation; the upper part of the femora is still poorly formed, and the position in this region is one of extreme valgus.

The Operation of Intertrochanteric Osteotomy

(Cinematograph Demonstration)

By NORMAN CAPENER, F.R.C.S.

THE purpose of this cinematograph demonstration is to encourage other members of this Section to describe similarly their operative methods. Surgical demonstrations to large audiences in operating theatres are not very satisfactory. With the cinematograph, however, particularly with the employment of the newer colour processes, the various steps can be shown in a manner that usually is available only to those actually assisting at the operation.

Intertrochanteric osteotomy, like subastragaloid arthrodesis, is an example of a procedure that may be considered fundamental. Upon these operations have been built up a variety of other procedures serving different purposes but with a common principle.

I do not suppose that there can be anything very original in my approach. I have used it for five years and demonstrated cases to this Section at Exeter in June 1937. The method is equally applicable for both intertrochanteric and subtrochan-

teric osteotomy in congenital coxa vara, in the Lorenz bifurcation for unreduced congenital dislocation of the hip, for ununited fracture of the neck of the femur, for the bifurcation operation suggested by McMurray (as in the present demonstration)

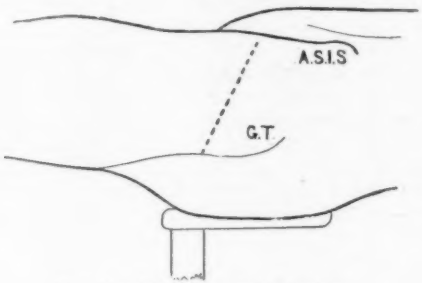


FIG. 1.—Side view of skin incision.

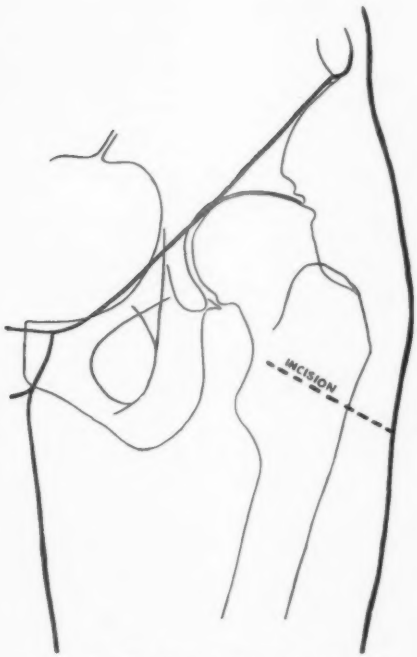


FIG. 2.—Showing relation of incision to neck of femur.

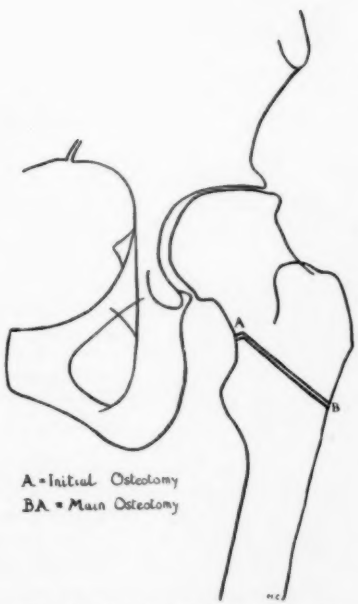


FIG. 3.—Showing sites of osteotomy.

for osteo-arthritis of the hip-joint ; it is suitable also for the insertion of a tri-fin nail for either fresh fractures of the neck of the femur or arthrodesis of the hip-joint. It also would be admirably suited for Brittain's method of arthrodesis by ischio-femoral synostosis.

My view is that the ordinary Smith-Petersen approach to the hip-joint is unnecessarily extensive for these purposes, and that the vertical lateral incision through the muscles does not give good access to the inner aspect of the neck of the femur.

The essential feature of the operation is an oblique incision through the anterolateral aspect of the thigh at the level of the lesser trochanter. The tensor fascia femoris muscle is divided transversely in this line and the vastus muscle stripped downwards subperiosteally from the front and sides of the femur. A narrow bone lever is now passed inwards beneath the rectus femoris muscle and the lesser trochanter identified ; the lever being passed above or below as required, then acts not only as a retractor but as a land-mark along which a narrow chisel may be passed and driven into the inner side of the neck of the femur before making the main osteotomy cut. This is an important point, reducing the risk of splintering the inner aspect of the femur, a relatively common occurrence when dealing with the rather brittle bones of

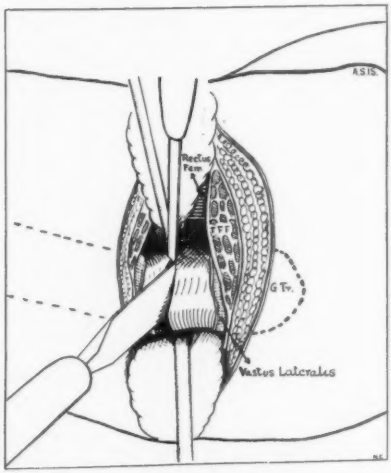


FIG. 4.—Diagrammatic tracing from moving picture : showing exposure of inner side of femoral neck by division of the tensor fascia femoris muscle.

senility. This chisel being firmly implanted, a broad chisel is then used and hammered through the femur from the outer side using the first chisel as a point of aim. A clean osteotomy is thus performed and, with the broad chisel in position, the shaft may now be readily levered inwards, if required. On the other hand a further cut may be made on the outer side so as to remove a wedge for the correction of coxa vara.

For the guidance of those preparing similar demonstrations I would stress that the surgeon should carry out his manœuvres in the same deliberate manner as at a normal operation, but should do so rather more slowly than usual. There is otherwise a tendency to repeat little steps in the action which on viewing gives the unfortunate effect of uncertainty.

Needless to say colour films specially prepared for artificial light are necessary, and in the present demonstration Kodachrome A was the material employed.

Fractures of the Shaft of the Humerus

By K. H. Pridie, F.R.C.S.

These fractures have gained a bad name, as non-union is said to be more common here than anywhere else in the body. Most of the trouble with fractures of the shaft of the humerus come from over-treatment and not from the original accident. Actually, in my opinion, of all fractures these are the easiest to treat if it is borne in mind that shortening up to 3 in. causes no permanent disability provided there is no stiffness of the joints (as Mr. Griffiths points out in his book " Injury and Incapacity ").

Surgeons treating these fractures are often unduly perturbed by the X-ray appearances. I hope to demonstrate in the following films how perfect results can be obtained when the skiagrams do not appear, to a lay mind, to show a good position.

The cause of non-union in these fractures is often due to traction. The stronger and the longer traction is applied the greater likelihood there is of non-union. Traction by means of a pin through the olecranon process is to be avoided at all costs. The following cases were examined for insurance companies, and illustrate what not to do. All these cases were treated by traction, and some of them later by operative treatment.

A cinematograph film was shown which demonstrated a simple method of treatment of fractures of the shaft of the humerus. It showed cases during and after removal of plaster casts and the final results.

The film also demonstrated how reduction is simplified by the use of local anæsthesia and gravity.

An attempt is made to show that traction need not be used in fractures of the humerus and, in fact, is often contra-indicated. Cases where traction was used with resulting non-union were shown ; also cases, following open operation, showing pseudo-arthrosis. The results of a bone-grafting operation in a case which had pseudo-arthrosis for six years was also shown in the film.

Case 1.—Mrs. M. Case of spiral fracture of the upper and middle third of the humerus. This was a simple fracture which, if left completely alone, would have healed firmly with a good result in six weeks. An enthusiastic surgeon, however, decided to fix the arm by open operation. Two Parham Martin bands were placed around the shaft of the humerus. The X-ray result was 100% perfect. The clinical result one year later was a pseudo-arthrosis and a flail arm, a tragedy, when no other treatment than a sling would have produced a perfect clinical result.

Case 2.—Aged 40. Fracture of the lower third of the humerus. Transverse in type and 3 in. above the elbow-joint. The patient was taken to hospital and treated by skin extension in a Thomas arm splint. After one week this was changed to extension in flexion. A Steinmann pin was put through the olecranon process, 20 lb. was applied to the olecranon. After six weeks of this traction the fragments were about ¾ in. over-pulled, there being a gap between the two fragments. As no sign of union had taken place it was decided that something must be done. A beef-bone plate was placed between the two fragments, and screwed into position with six screws. I first saw this man one year following the accident. The condition on examination was as follows :—

> The patient's left arm was held in a sling at right angles, the forearm being in full supination and only the tips of the fingers showing as the arm and hand were bound to a Cramer wire splint. There was very little movement in the fingers or thumb and the wrist, elbow and shoulder joints were stiff. No movement at all could be found in the elbow. The X-rays which the patient brought with him showed perfect anatomical alignment, the two bone ends held together by a posterior bone plate in good position.

Case 3.—R. B. Fractured lower third of the humerus. Treated two years by prolonged traction until despair of union, and then told to wear an arm corset. Condition on examination

showed a pseudo-arthrosis in the middle of the humerus. It was surprising what this patient could do with his arm. There was, however, no strength in the arm, except for pulling objects. The patient was a schoolmaster, and he was luckily still able to earn his living.

The lesson to be drawn from this case is as follows : Firstly, this patient is suffering from the results of treatment and not from his original accident, which although severe would have given a very reasonable result, probably over 80% perfect in one year if the following treatment had been adopted : The arm should have been suspended from a collar and cuff and action movements to the fingers and shoulder and radio-ulnar joints commenced immediately. After three weeks, gentle assisted movements should have been started in the elbow-joint. Secondly, the stiffness in the fingers, wrist and shoulder is due to prolonged disuse and traction through the elbow-joint. Thirdly, the irreparable damage to the elbow-joint is due to : (*a*) Traction for six weeks. (*b*) An operation of considerable severity in the close vicinity of a joint.

Everyone is agreed that the factor to aim for is good clinical results. The beautiful workmanship as shown by X-rays immediately after the operation may impress the patient, at the time, but what the patient really requires eventually is a good functional arm, no matter what the X-ray photographs look like. I always try to teach students that provided the clinical picture is good and the arm looks anatomically perfect, the X-ray appearances can be neglected.

Inexperienced surgeons are apt to be frightened by X-ray pictures. So great can be their fright that they feel bound to do something, whether the result of that something is worth while does not matter. The lay public are always delighted at the thought of an operation.

Section of Physical Medicine

President—K. R. Collis Hallowes, M.B.

(*January* 20, 1939)

Physiological Aspects of Rheumatism

By Professor Samson Wright

(*Department of Physiology, Middlesex Hospital Medical School*)

It is proposed in this paper to discuss such physiological principles and facts as may be of value in understanding some of the symptoms and signs of rheumatism, and critically assessing the methods of treatment which are in vogue, or which have been suggested. Rheumatism is a disease which is protean in its manifestations; further, when treatment is attempted, many systems or parts of the body may be subjected to vigorous onslaught. It is inevitable, therefore, that, in this paper a wide field should be covered somewhat superficially. Special attention will be paid to the following topics: (1) Mechanism of pain, particularly that arising in muscle. (2) The metabolism of skeletal muscle, and the properties of muscle extracts. (3) The interchange of fluid between blood and tissues, and the flow of lymph. (4) A critical analysis of the rational basis of massage. (5) The effects of reactive hyperæmia and of heat. (6) Physiological aspects of artificial hyperpyrexia.

Mechanism of Somatic Pain

The various encapsulated nerve-endings present in the skin are concerned with the sensations of heat, cold, and touch. The muscle spindles in muscle and the organs of Golgi in the tendons are stimulated by changes of tension, whether these are produced actively as a result of contraction, or passively by means of stretch. Pain sensibility in the skin is subserved both by free nerve-endings and by plexuses. The free endings are derived from both small myelinated and unmyelinated nerve-fibres. The former often penetrate the epidermis, and may end finally between the cells or actually *in* the cytoplasm of the tissue cells. This observation is significant, as the nerve-endings would thus be readily affected by changes in cellular metabolism, such as might be produced by a noxious agent. Woollard (1935, 1936) has also described unmyelinated plexiform networks in the subepidermal layers of the human skin. He suggests that sharply localized epidermal pain may be mediated by the more superficial fibres, and that less accurately localized pain is due to the fibres in the dermis. It is important to remember, however, that stimulation of sensory receptors other than those specifically concerned with pain cannot give rise to pain sensation. Thus, if a needle is inserted forcibly into a Meissner touch corpuscle, though it must undoubtedly cause intense stimulation, it evokes no conscious sensation other than that of touch or pressure. Little is known about the pain nerve-endings in muscle. According to Hinsey (1927, 1928), free nerve-endings are found round the blood-vessels in muscle and in the aponeurotic sheaths, and subserve pain in these localities.

Physiological investigations during the last decade, especially those of Adrian (1928, 1931) in this country, have greatly clarified our ideas of the mode of action

of the sensory organs, especially those in skin and muscle. Though there is still some uncertainty about the exact anatomical identity of the endings subserving the various modalities of sensation, there is no doubt that in each case there is a specific type of nerve-ending which responds to an appropriate and specific stimulus, and to none other. The quality of a sensation depends on the properties, largely not understood, of the region of the brain in which the impulses from the sense organ end. Thus, activation of the appropriate region of the occipital cortex gives rise to a sensation of sight, whether it is due to a light falling on the eye, artificial stimulation of the optic nerve-trunk, or irritation of the cortex itself. In the case of pain sensibility there is considerable doubt whether the cortex mediates the sensation, and it is more probable that its seat is mainly in the thalamus. The intensity of the sensation depends on the frequency of the impulses set up in the peripheral sense organ, and this may vary from a few to several hundred per second. The extent of the area stimulated is judged from the number of afferent fibres simultaneously activated. Less is known about the way in which sensation is localized, but probably it depends on the anatomical connexion between points in the peripheral sensory field and special groups of cells in the sensorium.

The sensation of pain is of especial concern to us here. It is undoubtedly a specific sensation, and not a mere intensification of other sensations. Lewis (1938) suggests that a complete description of pain should comprise a statement of " severity, kind or quality, and relation to time, locality and the circumstances in which it is felt ". Severity cannot be considered in great detail because it is too dependent on the patient's emotional and mental make-up to be gauged with any accuracy. The duration and the time-intensity curve is of great diagnostic value. Localization of the pain, though important, is difficult when one deals with the deeper visceral and somatic structures. Detailed information on this point is not readily elicited when much time has elapsed since the pain was experienced. It is, however, most important to assess the *quality* of pain. Lewis has presented evidence that three kinds of somatic pain exist, coming respectively from skin, muscle, and tendon, and differing qualitatively in their characteristics. Skin pain is always of the same quality, whether produced by pricking, burning, passage of an electric current, or the application of irritant poisons. The short, painful sensation produced in these ways is best known as pricking. More prolonged sensation of the skin set up in this way gives rise to a burning pain, whether it is due to heat or not. The muscles can be the seat of pain which is disagreeable, continuous, perhaps fluctuating in intensity, diffuse and difficult to locate ; though indescribable, it is quite different from skin pain. It can be produced by exercising a muscle under ischæmic conditions, squeezing the muscle violently or injecting into it hypertonic, or acid isotonic, saline solutions. Muscle pain may be referred to distant parts. The third kind is web pain, because it is elicited by pinching the short web of skin between adjacent fingers. Similar pain is elicited by appropriate stimulation of tendon or periosteum.

Kellgren (1938) has drawn renewed attention to the presence of tender spots in myalgia or fibrositis which, when pressed upon, give rise to diffuse widespread pain similar to that from which the patient suffers during his attacks. This more generalized pain is of a referred character. When the tender spots are infiltrated with a local anæsthetic both the local and referred pain disappear, sometimes for as long as one to four weeks. This may account for the beneficial effect of massage and of radiation therapy applied to localized tender spots which are probably the actual foci of the disease.

Lewis (1932) has studied more particularly the mechanism of ischæmic muscle pain. The circulation to an arm is entirely occluded and exercise is carried out by performing a gripping movement with the hand at the rate of once per second. Pain sets in in about 30 seconds and is intolerable in 70 seconds. Though the pain is diffusely felt, it is most marked in the muscles. It is not due to vascular spasm

because, after occlusion, the blood-vessels lose their tone. It is not due to muscular tension because it is continuous and is not accentuated during the phase of contraction. It is the result of activity because it is related to the amount of exercise which is performed. It is not due to local anoxia. If the limb is exercised to a point short of pain and the occlusion kept up, no pain develops, although the anoxia is becoming progressively more intense. It is suggested that activity liberates a pain-producing factor (P) which normally passes into the tissue spaces and is removed by the blood-stream. This substance accumulates in conditions of ischæmia, and so gives rise to pain. If pain has appeared and the ischæmia is maintained without further exercise, the pain gets no worse. On releasing the circulation the pain rapidly disappears.

Muscle Metabolism (*see Eggleton*, 1935)

Our ideas on muscle metabolism are very much more indefinite and less dogmatic than they used to be. It was thought at one time that the essential chemical change which liberates energy in muscle, and so enables work to be performed, was the breakdown of glycogen. Little attention was paid to the other and perhaps more specific constituents of muscle, though it was probable that they served some purpose. The schema below gives in a very diagrammatic form some of the principal reactions and their time relationships.

Schema of Muscle Metabolism

A.—Reactions occurring when muscle is stimulated to contract in an atmosphere of nitrogen.

(1) Adenyl pyrophosphate $\rightleftarrows$ adenylic acid + phosphate.
(2) Creatine phosphate $\rightleftarrows$ creatine + phosphate.
(3) Glycogen $\rightarrow$ lactic acid.
(4) Lactic acid + muscle protein or other base $\rightarrow$ lactate.

All these reactions are exothermic and give out energy. They probably occur in the order indicated. In the case of the first two reactions, resynthesis of the original complex compound may occur even anaerobically if free energy is available.

B.—Reactions occurring when muscle is stimulated in an atmosphere of oxygen.

(1) All those given in A (1–4).
(2) Resynthesis of adenyl pyrophosphate and creatine phosphate.
(3) Conversion of lactate into (*a*) glycogen or (*b*) its combustion to CO_2 and water.
(4) Combustion of other foodstuffs (possibly fat) to CO_2 and water.

Reactions B2 and 3 (*a*) are endothermic (taking up energy), and 3 (*b*) and 4 are exothermic.

The schema is certainly a very incomplete representation of what really takes place, and there is no doubt that many hitherto unknown chemical reactions of considerable importance occur. Most of these interactions are coupled in the sense that the second stage depends on the occurrence of the first; many intermediate stages are passed through between the original substance and the appearance of the final end-product. Neither glycogen breakdown nor phosphagen breakdown are essential for muscle contraction, and it is uncertain whether adenyl pyrophosphoric acid is any more indispensable. As is shown in the schema, most of the reactions occur in the absence of oxygen, and oxygen is only necessary for the final recovery processes. As has been mentioned, some of the reactions liberate and others take up energy, but nothing is known about the way in which the free energy is converted into mechanical work. If a muscle is exercised excessively under conditions of inadequate blood or oxygen supply, fatigue sets in, leading finally to complete loss of excitability. Nothing is known of the causation of fatigue, except the negative

information that it is not due to the rise of H-ion concentration or to lactic acid accumulation. Even the cause of rigor mortis is unknown.

Extracts of muscle have been proved to contain choline or acetylcholine, histamine (probably derived from carnosine which is β-alanyl-histidine) and adenosine (from adenyl-pyrophosphate) (*see* Gaddum, 1936). These substances have complex and important pharmacological activities, but share one property in common—namely that on injection they lower the blood-pressure and produce dilatation of blood-vessels. It is possible that, when tissues are damaged, some or all of these substances are liberated. It may be that even quite trivial injuries such as those inflicted during massage may act similarly. Muscle extracts may also contain a blood-pressure raising (pressor) substance of undetermined identity, which is related to tyramine.

Reference has already been made to the " P " factor which Lewis postulates as being liberated in muscle during ischæmia, and which is responsible for the associated pain.

Lastly, mention must be made of the work of Alam and Smirk (1938 *a*, *b*, *c*, *d*). who have shown that muscular activity in man leads to local formation of still another agent which stimulates sensory nerve-endings in the active area and so reflexly raises the blood-pressure and increases the pulse-rate.

The Interchange of Fluid between Blood and Tissue Spaces and the Flow of Lymph

The proper nutrition of the tissues depends very largely on their blood supply, and so it will not be out of place to summarize briefly the main factors regulating the state of the circulation in skin and muscles (*see* McDowall, 1938).

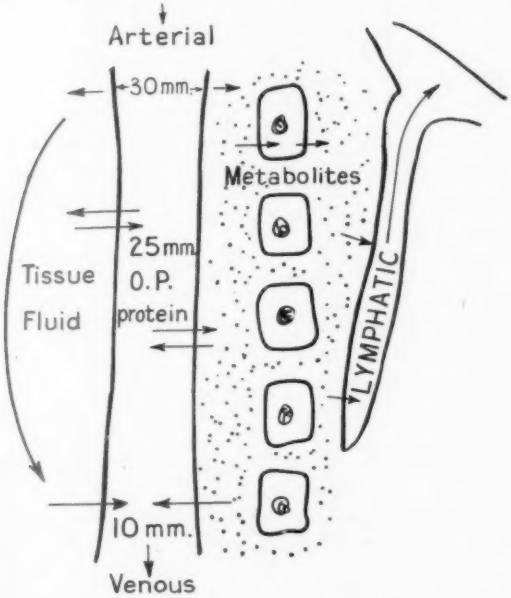
The skin is supplied by many sympathetic nerves (almost wholly vasoconstrictor in character) which control not only the arteries but also the capillaries and venules. There are in addition a few sympathetic dilator nerves, and other dilator fibres (ill-understood), in the posterior nerve-roots. The skin vessels are markedly affected by changes in the tonic activity of the vasomotor centre and are, of course, readily accessible to local mechanical, thermal and chemical stimuli.

The blood supply to the muscles is regulated partly by local products of activity and partly by a general adjustment of the circulation. If the exercise is moderate in character and restricted to a small part of the body, the formation of dilator substances in the active areas increases the blood supply adequately to provide for the greater needs. If the activity is more severe and general, a complex adjustment of the entire cardiovascular system occurs, which leads, on the one hand, to a much greater cardiac output and, on the other, to a diversion of most of this outflow to the active regions. The blood supply to the muscles may increase eight or ten-fold under these circumstances.

The factors principally concerned in regulating the actual fluid exchanges between the blood and the tissues are summarized in the diagram on p. 11. The plasma protein concentration is 6–8%, and exerts an osmotic pressure of about 25 mm.Hg ; the corresponding protein concentration in the tissue spaces is believed to be small, and so its osmotic pressure can be ignored. The blood-pressure at the arterial end of a capillary is of the order of 30 mm.Hg, and at the venous end about 10 mm. The hydrostatic pressure in the tissues is approximately atmospheric. The salts of the blood and tissues can be ignored because the capillary membrane is freely permeable to them and allows them to pass through, so that normally these concentrations are the same on the two sides. In a resting tissue the sequence of events is as follows : at the arterial end of the capillary the outward driving force of the capillary pressure exceeds the inward pulling force of the protein osmotic pressure, with the result that fluid (containing all the dissolved crystalloids and gases of the plasma) is driven out into the tissue spaces. The tissues thus receive their supplies of nutriment. At the venous end of the capillary the balance of forces is

reversed, the capillary blood-pressure now being less than the protein osmotic pressure. Consequently fluid flows in from the blood into the tissue spaces, carrying with it again all the crystalloid constituents, including the various waste products which have been made in the tissues. Any factor which dilutes the blood tends to reduce the protein osmotic pressure and raise the capillary pressure, and so leads to a greater outflow into the tissue spaces. This occurs after drinking large quantities of water, and more so after drinking saline, or when saline is given *per rectum* or subcutaneously. Conversely, fluid loss from the skin in sweating, from the bowel in diarrhœa, or from the lungs in excessive breathing, leads to a withdrawal of fluid from the tissue spaces.

During muscular activity the amount of exudate pouring from the blood into the tissue spaces is enormously increased, and may amount to 2 c.c. per 100 grm. of



tissue per minute. The fluid content of the muscle may increase by about 20%. The main factors involved are (i) an immensely greater blood supply due to general circulatory adjustments and local vasodilatation; (ii) an increased blood-pressure throughout the length of the capillaries; (iii) an increase in the number of patent capillaries and dilatation of those previously open; (iv) increased capillary permeability; (v) the accumulation of (hypothetical) osmotically active products of metabolism in the tissue spaces (cf. Samson Wright, 1936).

The rôle of the lymphatics is still very puzzling (*see* Drinker and Field, 1933). They begin as minute channels in the tissues which are completely clothed by an endothelial lining. It is not known what forces are responsible for transferring fluid from the tissues into the lymphatics. Judging from animal experiments, the resting flow along lymphatics is small. With the animal lying on the table and a cannula inserted into a lymphatic in the leg, no flow whatever occurs except as a result of massage. During muscular activity, the lymph-flow greatly increases, as it

then constitutes the major channel for draining the excess fluid away. The movement of fluid along the larger lymphatics depends on the same factors (in the main) as promote the venous return. These are muscular movements massaging the vessels, aided by the valves in the lymphatics; the descent of the diaphragm raising intra-abdominal pressure, and so helping to expel the lymph from the abdomen; and lastly the negative intrapleural pressure which aspirates the lymph into the thorax, and so finally into the great veins.

Critical Analysis of Massage (*cf. Mock, Pemberton and Coulter*, 1934)

The movements employed in massage are differently described and classified by different authors. Mennell (1934) recognizes three main varieties of movement: stroking, compression, and percussion movements. Further subdivision is suggested by other writers and considerable confusion in terminology seems to exist.

Stroking movements may be superficial or deep. When the movement is centripetal it is often called effleurage; when in the reverse direction it is simply described as stroking. Mennell argues that the direction of superficial stroking is immaterial from the therapeutic standpoint, so long as it is slow, gentle, and rhythmical in character. Others regard centrifugal stroking as irrational and ineffective. Mennell does, however, insist that the movements used must always be in one direction only. It is advocated, however, that deep stroking massage should always be performed centripetally only.

Extensive physiological and therapeutic effects are said to result from these procedures (cf. Copestake, 1933).

Superficial stroking is said to improve the cutaneous circulation, especially by promoting the flow in the superficial veins and lymphatics; to facilitate interchange of tissue fluids; to increase the nutrition of the tissues; and to remove products of fatigue or inflammation. It is even said to accelerate gaseous interchanges between the skin and the external air. Great stress is laid on the reflex effects resulting from the special kind of sensory stimulation employed. These claims must be examined critically in the light of current physiological knowledge. Very light stimulation acts directly on the capillaries in the skin, causing them to contract with resulting pallor. This reaction accounts for the "white line" which is obtained when the skin is gently stroked. The response is independent of the integrity of the local nerve supply, and is due to the independent contraction of the capillary wall in response to mechanical stimulation. More vigorous stroking, especially in susceptible subjects, produces cutaneous vasodilatation of varying degree. This type of reaction can be conveniently studied when the skin is vigorously stroked or scratched. The complete reaction consists of the so-called "triple response" of Lewis (1927), namely capillary dilatation, ateriolar dilatation, and whealing; commonly only the first two reactions are obtained. The triple response is attributed to local liberation of histamine from a precursor in the skin. The capillary dilatation which accounts for the reddening of the skin is due to a direct action of histamine on the capillary wall. The arteriolar dilatation is due to a local axon reflex; histamine stimulates sensory nerve-endings and impulses pass through cutaneous nerve plexuses to reach adjacent arterioles. As a result, the blood-flow through the skin is increased, and the cutaneous temperature may rise by 1° or 2° F. The permeability of the capillaries is increased, and, as their internal pressure is simultaneously raised, there is a greater exudation of fluid into the tissue spaces. In susceptible subjects œdema or wheal formation may take place because of the great volume of fluid which is allowed to escape from the blood; this fluid is abnormally rich in plasma proteins. If the stroking is centripetal in direction, the flow in the superficial veins and lymphatics may be hurried on, but the effect is unlikely to be significant when the circulation is normal. It might, however, be of greater value when the circulation is obstructed or impaired. It is probably inaccurate to stress excessively the effects on the lymphatics even in patho-

logical states. Judging from animal experiments, the normal resting rate of flow in the lymphatics is very low compared with that in the veins. Lymph-flow can be measured in animals in the larger vessels by appropriate cannulation. A substantial flow is obtained in certain circumstances, e.g. when the capillary walls are abnormally permeable, when there is a large decrease in plasma protein concentration, or a great increase in capillary and venous pressure. These are conditions which are mainly pathological, and act by increasing tissue fluid formation. Physiological activity is undoubtedly the principal *normal* factor controlling the process. Lymph-flow is, however, influenced to some extent by massage or passive movement. The flow obtained by massage from the hind paw of an anæsthetized dog varied from 0·3–3·6 c.c. per ten minutes, which is very small compared with the blood-flow. The weight of the part was about 200–300 grm. In some animals practically no lymph at all can be obtained from lymphatics under normal conditions.

Practically nothing is known about skin metabolism, so it is idle to speculate about its possible modification by massage, or about the effects of massage on the rate of removal of fatigue or other noxious products. Sweat secretion is not significantly increased by local vasodilatation, but sebaceous secretions may be expressed.

It is difficult to dogmatize about the reflex effects produced by massage. Adequate and properly controlled clinical observations appear to be scanty. In experimental animals, sensory nerve stimulation produces effects which vary with the nerve used, the kind, strength, and duration of stimulation, and the state of the animal. The blood-pressure and heart-rate may rise or fall; there may be slight modification in one direction or another of sympathetic or parasympathetic tone, with resulting changes in visceral activity; breathing may be profoundly altered. Similarly, in man, it may be supposed that the effects will depend on the exact mode of stimulation employed, and will vary with different kinds of mechanical, thermal, or chemical stimulation. This problem at present seems to demand further investigation rather than extensive discussion.

Impulses set up in the skin will reach the subcortical or cortical levels and modify activity there. Remarkable curative effects are claimed for superficial stroking in conditions labelled neurasthenia, and in insomnia. If the claims are justified, they cannot as yet be accounted for by any known physiological considerations. The psychologist may, however, suggest that the manner and personality of the masseur may be of especial importance.

Deep stroking will doubtless tend to produce a greater degree of cutaneous vasodilatation and greater mechanical effects. It may influence mechanically the activity of underlying viscera also. It is conceivable that the slight immediate tissue damage that occurs may liberate histamine and other metabolites, depressor as well as pressor, in sufficient amounts to enable them to enter the blood-stream, and so produce effects at a distance.

Compression movements include kneading, friction, and petrissage. Percussion movements, which may also be considered here, include hacking, clapping, and beating. Somewhat sweeping claims are made for these procedures. Friction is alleged to help absorption of fat in fatty tissues. This seems to be wholly without foundation. Mechanical treatment of this kind can only cause removal of local fat by breaking down the cells of the adipose tissue, so that the stored fat is liberated. This can only occur when grave local injury is inflicted. Even then the liberated fat would remain locally. If it were absorbed, it would only be deposited elsewhere, and not be finally disposed of. As a treatment for obesity it seems wholly irrational.

Compression and related movements are said to influence muscular activity promoting contraction or relaxation. Fatigue and other waste products are said to be removed: among those specified are uric and butyric acids, which are never found in muscle, and carbonic acid and lactic acid, which diffuse freely into the blood and can only be influenced by increasing the local circulation. The local vascular

and lymphatic circulations are improved, and the nutrition of the part is said to be maintained during a period of forced inactivity. It is claimed that muscular activity set up by massage is preferable to that occurring during voluntary movement, because the latter involves what is called "exhaustion of nervous energies". Stress is laid on more indefinable effects, such as an increased sense of comfort and well-being in the muscles. It is alleged that conduction in spinal nerves is modified, being facilitated by weaker stimulation and depressed by stronger. The activity of the local vasomotor nerves may be modified, body temperature raised, and a complex variety of reflex results produced.

It is necessary first to clear the ground to some extent by disposing of those claims that have been disproved. General vigorous massage does not increase O_2 consumption, CO_2 output, or heat production, unless there are associated movements of the muscles. This means that the degree of muscular activity induced locally or generally is too small to be measured. There is no change in the blood lactate or inorganic phosphate. The composition of the urine is unaltered, and there is an insignificant increase in urinary output, which may be due to massage of the abdominal vessels. The claims usually made that muscle wasting is prevented or muscle nutrition improved by massage when unaccompanied by movements seem to require more rigorous proof. Some local effects are undoubtedly produced in the muscle. Massage of resting muscle in animals produces a definite increase in local blood-flow, but it is small compared with that resulting from activity, or occurring during passive hyperæmia. Chemical agents may be liberated or expressed into the blood, and may produce local or general effects. In this connexion it is worth again drawing attention to the many metabolites, both known and unidentified, that are liberated during muscle activity, or during muscle damage or ischæmia. Some or all of these might be liberated by massage. The blood-pressure might be raised by mechanically increasing the venous return, or lowered by increasing the vascular capacity locally. It is uncertain whether direct mechanical stimulation of this kind can produce a direct muscular response, say, in denervated muscle in which reflex reactions are of course excluded; the point is worth looking into. Particular attention must be paid to reflex effects, both on the muscles stimulated, on muscles elsewhere, and on other organs. Experimentally, we know that stretch of a muscle may cause reflexly local contraction or reflex relaxation. If the stretch is within certain moderate limits, reflex contraction results, which is the basis of the tendon reflexes and of muscle tone; if the stretch is greater in extent, then reflex relaxation occurs, as shown in the so-called lengthening reaction of Sherrington. More remote effects may also be produced. Stretch of the hamstrings reflexly inhibits tone in the antagonistic quadriceps; stretch of the quadriceps produces contraction of the opposite quadriceps. Many more distant muscular changes could be specified. Experimentally, stimulation of muscle afferents produces the same complex and variable autonomic responses as were noted in the case of the skin. These reactions require detailed study under suitable conditions in man. Here, too, it would be wiser to refrain from commenting on the psychological effects of these procedures.

Effects of Local Heat

Here we are on much surer ground. If heat is applied to a limb, or if the limb is plunged into hot water at a temperature of 40°–45° C., marked cutaneous reddening results. The vasodilatation observed is due to a number of factors. Heat acts directly on the walls of the superficial vessels; there is also a reflex dilatation through the central nervous system resulting from stimulation of the heat nerve-endings; lastly, there is local liberation of a histamine-like substance (especially with higher temperatures) leading to the usual triple response. The beneficial effects on cutaneous blood-flow and tissue-fluid interchange would be identical with those resulting from vasodilatation produced by any other means.

Less is known about the effects of external heat on the circulation in the muscles. The temperature of the deeper structures rises slowly, because of the insulating action of the fatty subcutaneous tissues. Such dilatation as may occur in the muscles as a result of local heating must be brought about almost entirely through reflex channels.

Reactive Hyperæmia (*see Lewis and Grant*, 1925)

Reactive hyperæmia is a phenomenon of great physiological interest, and is probably worthy of more extensive clinical use. The essential facts are well known. The circulation to a limb is obstructed for a period of, say, five minutes by means of a tourniquet or a suitably inflated blood-pressure cuff. The obstruction is then removed. Within a few seconds the skin flushes brightly, attaining its maximum colour at once, and the volume of the pulse is increased. The hyperæmia declines somewhat after twenty to thirty seconds, and is gone in a few minutes. The associated changes can be measured quantitatively by enclosing the limb in a plethysmograph. The inflow of blood when the circulation is released is determined by measuring the degree of swelling which is obtained during a short period of venous obstruction at 55–70 mm.Hg pressure. The response after occlusion is affected by a number of factors: (1) The temperature of the plethysmograph or of the outside air: at 18° and 41° C. the resulting increases in volume may be 2 c.c. and 15–20 c.c. respectively. (2) The duration of the occlusion: the degree of hyperæmia is greater and more lasting as the period of occlusion is prolonged.

Occlusion lasting for ten minutes produces a greater degree of hyperæmia of the limb than does soaking it in water at 43°–44° C. for half an hour; it also compares fairly well quantitatively with the hyperæmia resulting from muscular effort. In the latter case, however, it is more persistent and affects the muscles chiefly, rather than the cutaneous vessels.

Reactive hyperæmia also follows venous obstruction. On releasing the occlusion there is, of course, an initial decrease in limb volume, owing to the escape of the blood stored up in the distended capillaries and veins. This is accompanied, however, by an increased inflow of considerable magnitude. The following data of Lewis and Grant (1925) are of interest: The resting inflow per 100 c.c. of tissue per minute was 10 c.c.; after venous congestion for one, five, and ten minutes, it rose to 16, 41, and 58 c.c. respectively.

The vessels concerned in reactive hyperæmia are (1) the capillaries which dilate, accounting for the flushing of the skin, and (2) the arterioles which dilate, accounting for the increased blood-flow and pulse volume and the local rise of temperature. These changes are probably due to accumulation during occlusion of dilator metabolites, known or unknown. We may go some way towards identifying the agents concerned (Barsoum and Gaddum, 1935). If a limb is made ischæmic in animals by blocking the arterial supply, the venous outflow is found to contain members of the adenosine group and histamine in excess. These, and local acidity, are probably the main agents concerned. In addition, these factors may be responsible for promoting the establishment of a collateral circulation when the obstruction is of a lasting character. In venous obstruction there must also be an increase in tissue fluid formation, owing to the raised capillary pressure and therefore a raised filtering force. When reactive hyperæmia follows, the dilatation of the arterioles leads to a rise of capillary pressure from the other (arterial) end; the increased blood-flow, too, must accelerate tissue fluid interchanges. Arterial occlusion only increases these interchanges subsequently, during the period of reactive hyperæmia. As was previously pointed out, local heat leads to vasodilatation and increased capillary pressure; but the increased tissue fluid formation in these experiments is presumably mainly in the skin, and not in muscles, as in the ischæmic experiments.

Other methods of increasing fluid interchanges have been touched on previously; thus ingestion of water, especially of saline, leads to temporary filling of tissue spaces,

from which fluid is subsequently withdrawn. Extensive sweating causes withdrawal of fluid from the tissues which must subsequently be replenished. A simple rise of arterial pressure, unattended by activity, causes no change in fluid interchanges or lymph-flow unless it is associated with great congestion of the part, of such magnitude that it leads secondarily to a rise of venous pressure.

Pyrexial Treatment (*see Neymann*, 1938)

The treatment of rheumatic conditions by means of elevation of the general body temperature has been advocated and practised increasingly, especially in America. Normal body temperature depends on the accurate balancing of heat formation and heat loss. By increasing the former, or diminishing the latter, body temperature is elevated. If a man is completely insulated so that he neither loses heat to, nor gains heat from, the exterior, the body temperature would rise by about 2° C. per hour simply as a result of retention of the heat liberated from normal resting metabolism. The rise is, in a sense, a small one, owing to the very large heat capacity of the water which constitutes nearly 80% of the body-weight. If the body were made of steel, the rise of temperature would be eight times as great. The high heat capacity is, of course, shared by blood, which enables it to transport large amounts of heat for a given rate of flow. It also enables small temperature gradients to lead to large heat exchanges.

Heat loss in the normal person at rest occurs by radiation and convection from skin (73%), evaporation of water from skin (14%) and lungs (7%), warming of expired air (4%), and of excreta (2%).

Loss of heat from the lungs depends on temperature, humidity and volume of respired air, which is expelled saturated at 33° C. The resting water loss at rest from the lungs is about 400 c.c., and from the skin 800 c.c.

Evaporation from the skin is the main process which is adjusted to increase heat loss. It takes place in two ways :—

(1) By insensible perspiration. This goes on at a fairly uniform rate over the whole body surface, except for a few regions such as the face, neck, dorsum of hand, soles and palms, where it is substantially higher in increasing order. It varies to a limited extent only. It consists of the physical passage of water by diffusion of tissue fluid through the epidermis ; the amount of insensible perspiration is not diminished in people without sweat-glands.

(2) By sweating (cf. Kuno, 1934). There are two kinds of sweat-glands in man : (*a*) *Eccrine*, distributed generally over the surface of the body, excreting a dilute solution of sodium chloride, urea, and lactate. (*b*) *Apocrine*, large glands found mainly in the axillæ and pubis, and forming a secretion of variable composition.

Sweating is mainly produced reflexly by stimulation of heat nerves, but occurs to some extent also from a rise of brain temperature. The distribution of sweating differs in muscular exercise and in hyperpyrexia. In the latter it takes place mainly on the forehead, dorsum of hand, chest and neck, thigh and forearm, axilla, palms and soles, in descending order. In activity or hyperpyrexia, heat loss from evaporation may account for 80% of the whole (as against 14% at rest).

It is well known that a considerable degree of hyperpyrexia may occur in violent exercise, depending on its severity and duration and the facilities for heat loss. Temperatures of 103° F. or over may be attained. In resting persons, pyrexia can be produced by drugs which stimulate metabolism, but toxic doses have to be employed. Usually a combination of heating and impaired heat loss is employed.

If a patient is immersed in a hot bath, loss of heat from the submerged regions of the skin is arrested or converted into heat uptake by the greatly increased local blood-flow. The process of heating is relatively slow, and the temperature attained is limited by the tolerance of the skin to the damaging action of the hot water. It is suggested that the bath be at a temperature, initially (or, in less tolerant patients,

finally) of 110° F. (43·5° C.), which is maintained for one hour. When the temperature of the patient is within 1·5° of that aimed at, the bath temperature is gradually lowered till it equals the body temperature desired. A body temperature of 104° F. may be thus attained. Heating can also be produced by means of heated blankets, or by placing the patient in an insulated conditioned preheated bag.

The procedure mainly advocated now is to heat the body by means of penetrating high-frequency currents, combined with insulation to minimize heat loss. The body temperature can be raised more rapidly than with hot blankets, but not more rapidly than in a conditioned air cabinet containing moist air at a temperature of 120°–160° F. For a given rise of body temperature the pulse-rate is related to some extent to skin temperature. In fever, for instance, there is a rise of 8–10 beats per 1° F. rise of temperature. In pyrexia produced by electromagnetic induction, skin temperature is lower than with a similar degree of pyrexia resulting from the external heating, and the pulse-rate increase for any given body temperature is correspondingly less. It is interesting to note that ice applied to the skin lowers the pulse-rate when the rectal temperature is unaltered, or even if it is moving in the reverse direction. It should be borne in mind that in all forms of pyrexia the metabolic rate rises by about 7% with each 1° F. rise of body temperature. It is reported that body temperatures up to 107·6° F. can be maintained for hours by this means in robust subjects.

It is claimed for the electropyrexial technique that it is more flexible than the other procedures suggested, and that various types of body temperature curves can be obtained. Normally the temperature of the subcutaneous tissues of the thorax and abdomen is 2° F. lower than in the internal organs: this difference increases as one passes more distally in the limbs to a maximum of 5° F. This gradient persists to a greater extent in electropyrexia than in external heating, and is claimed to be of advantage.

The main changes taking place in the body during hyperpyrexia are as follows:—

(1) The pulse-rate may rise up to 160 per minute. It is interesting that Delaroche, who in 1806 exposed himself to an external atmosphere of 65° C., showed a pulse-rate of this order. The same effect can be produced by a hot bath at 110° F., with a body temperature of 104·6° F.

(2) The systolic blood-pressure is said to rise in electropyrexia, but may be seriously lowered (even down to 60 mm.) in the erect position with external heating. The diastolic pressure may fall even to zero.

(3) Too little is known about the electrocardiographic changes for dogmatic statements to be made.

(4) The cardiac output is increased, though exact measurements are not available. The circulation time which (using the sodium cyanide method) varies inversely with the output of the heart, may fall from the normal of 20 seconds to 6 seconds when the body temperature is 105·8° F.

There can be no doubt from the data just presented that the heart during hyperpyrexia is subjected to very considerable strain. The output is increased and the systolic blood-pressure is raised, with the result that the work of the heart is much greater than it is normally. Owing to the cardiac acceleration which is present, the duration of the diastolic pause is cut down so that the period available for recovery is diminished. Most serious of all, probably, is the great diminution in diastolic pressure which gravely affects the nutrition of the heart. The coronary inflow takes place almost entirely during *diastole*, and depends directly on the so-called mean blood-pressure (i.e. the mean between systolic and diastolic pressure). The great lowering of diastolic pressure must cause a diminished blood supply to the heart, with inevitable impairment of its efficiency. Lastly, it has to be borne in mind that the heart is subjected to these conditions of strain for periods up to eight hours. It is no wonder, therefore, that cardiac complications occur, and that stoppage of the heart is not unknown.

(5) Respiratory rate increases initially, but subsequently it may become irregular or Cheyne-Stokes in character; bouts of apnœa may occur of increasing duration (up to one minute) and frequency (every three minutes) interspersed with periods of hyperpnœa. Respiratory arrest may finally take place.

(6) Blood CO_2 may fall to 30 vols.% during the initial phase of over-ventilation, and considerable alkalæmia develops (pH 7·6).

(7) There are doubtful changes in the white cell count; an initial leucopenia followed by a neutrophil leucocytosis with young forms is described.

(8) The most important blood changes, however, are chiefly due to the immense secretion of sweat. The facts about sweat composition are complex. There may be large individual variations in the NaCl concentration in the sweat (e.g. ×2). As acclimatization occurs in hot environments, the NaCl concentration may fall from round 25 m-equiv. (0·9%) to 12–18 m-equiv. In one case (Dill, 1938) it fell in four days from 0·75% to 0·55%. This compensatory reaction is of importance as it helps to conserve sodium chloride in the body. This adaptation would presumably not occur during a bout of artificially induced hyperpyrexia. The sweat lactate concentration may be very high, up to twenty times that of the blood lactate.

Water loss from the skin may be 8–11 litres in five to eight hours. In the dry torrid heat of Boulder City, Nevada (38°–44° C. maximal shade temperature, humidity 6–30%), the sweat output was 79 litres in fourteen days (5·5 litres per day) with, of course, corresponding NaCl loss (cf. Dill, 1938). Unless adequately compensated for by drinking weak saline, dehydration and salt loss must result, with a diminishing of the blood volume and increasing viscosity. Although the concentration of the plasma electrolytes generally is increased, the plasma Na and Cl concentrations are diminished, owing to the extensive loss in the sweat. The total crystalloid osmotic pressure of the plasma is unchanged. The red cell count may rise, and so does the plasma protein concentration. The changes lead to the well-known heat cramps in muscles. The changes just described must, in the main, take place also during electropyrexia, though here, possibly, sweating may be less extensive.

It is clear that in these pyrexial experiments one is working at the extreme limit of tolerance, and a definite element of risk is involved. Of the discomfort experienced, both the literature and the patients' own stories are eloquent testimony.

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Section of Surgery

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[*November* 2, 1938]

DISCUSSION ON DIAGNOSIS AND TREATMENT OF NEOPLASMS OF THE TESTIS

Opener: **G. Gordon-Taylor, O.B.E., M.S.**[1]

Abstract.—Various clinical types of the disease; mistakes in diagnosis.—Methods of diagnosis, clinical and biochemical.—The undescended testicle, and its relationship to malignant disease. *Treatment.*—The diminishing field of operation, the value of X-ray treatment, and the improvement in the results therefrom.

Dr. W. M. Levitt: One of the main purposes of this discussion is to find the answer to the question: How are malignant growths of the testis best treated? My contribution deals mainly with this consideration, and although a final answer cannot yet be given, I hope to show that there are some definite lines that should guide us.

First of all, what should be the respective rôles of surgery and radiotherapy in the treatment of the commonest type of case, that of the uncomplicated testicular growth in an otherwise healthy man without demonstrable metastases? There is no doubt that in a great many the growth could be destroyed by X-ray treatment, and the end-results would probably not differ greatly from those obtained by a combination of surgery and irradiation. Nevertheless I would always advise removal of the growth (unless there is some good reason to the contrary), if only for the purpose of obviating the absorption of breakdown products of the growth which occurs under the influence of X-ray treatment, and which often causes quite severe toxic symptoms, especially if disintegration is rapid. This throws an additional strain on the patient's general condition, which is already being sufficiently tried by a prolonged course of radiations. To avoid this, the best time to do the operation is before the irradiation and not after.

Technical details of radiation treatment cannot be discussed here, but there are two questions that we must consider, for they are of great importance. Firstly, what should be the *scope* of the irradiation in these cases, and secondly, should X-rays or radium be used?

As regards the *scope* of the irradiation, the possibilities are many and the practice varied. We might confine our attention to the pelvis; we might extend the irradiation to the lumbar region on the same side, or on both sides; or we might extend the irradiation to include the mediastinal glands, the lung fields, or even to include the whole trunk. I think that most people are agreed that at least the pelvis should be irradiated. When, however, we come to regions farther afield, we should consider first whether it is worth while irradiating metastatic deposits in such areas, for after all, the treatment is only given on the assumption that metastatic deposits are

[1] Paper previously published: *Brit. J. Urol.*, 1938, **10**, 1.

present in a proportion of cases, though not clinically demonstrable. Here is a table giving the results of treatment in 18 cases of metastatic deposits from testicular growths treated in the Radiotherapeutic Department at St. Bartholomew's Hospital from 1930–35.

MALIGNANT DISEASE OF TESTIS TREATED BY X-RAYS.

Gross Disease Present at Time of Irradiation.

Year	Number treated	Alive Sept. 1938	Dead
1930	1	0	1
1931	0	—	—
1932	9	2	7
1933	4	1	3
1934	1	0	1
1935	3	2	1
	18	5	13

Survival for five years and over : Three out of 14, of which three are still living.

It will be seen from the table of 18 cases treated from 1930–35, five were alive in September 1938 and of those, four were without signs of disease.

I may perhaps be allowed to quote two cases in the above series as examples of the results that may sometimes be obtained from the treatment even of advanced cases.

The first of these was a man aged 36, who complained of a swelling in his left testis and of some pain and swelling in the left loin, together with loss of strength and loss of appetite. He was an ill man with an irregular mass in the left testis and a large mass 18 × 12 cm. in the left hypochondrium, reaching down to 5 cm. below the umbilicus and extending across the mid-line. The mass was hard, irregular, and very fixed. He was treated by the " X-ray bath " method, details of which I published earlier this year (*Brit. Journ. Radiol.*, March, 1938), in November and December 1933. In the course of the treatment, both the primary growth and the mass in the abdomen rapidly reduced in size, although they had not entirely disappeared by the end of the course.

After his treatment we lost sight of him until July of this year, when he came up to see me at the hospital, complaining of a slight recurrence of some of his abdominal symptoms. I thought I could feel some deep glands in his abdomen, but none of my colleagues could feel them. He had a further course of treatment, lost all his symptoms, and has now returned to his full work again. During the five years since his original treatment, this patient has been completely normal in every way and has done his full work as an engineer.

The second case is that of a man aged 32, sent to me at St. Bartholomew's Hospital in October 1933. He had advanced abdominal recurrences following an orchidectomy for a testicular growth a year previously. He was in great pain and had lost much weight and was passing blood *per rectum* and looked extremely ill. There were large masses in the upper abdomen and in both iliac fossæ, and there were enlarged glands in the hila of both lungs. X-ray treatment by the " bath " method resulted in the disappearance of the signs and symptoms of disease, and the patient remained in apparently normal health for one year, after which he got a recurrence in the epigastrium, which was also treated by X-rays. Following this treatment the patient again lost his symptoms and signs and remained perfectly well until last summer, when he got further recurrences in the abdomen and in the chest. He was again treated, and although the disease again yielded to treatment, his general condition is beginning to show the effects of repeated and prolonged courses of X-rays, and he is not so fit as I should like to see him. Nevertheless, until very recently he has been doing his full work except when interrupted by the courses of X-ray treatment.

From the results reported in the table and from the two cases described in particular, I think it is evident that metastases, even when generalized, originating from testicular growths, can be made to disappear for long periods by radiation treatment. There cannot be any doubt, therefore, that there is a good case for irradiating our post-operative cases for prophylactic purposes and applying the treatment even to remote regions such as the upper abdomen. In order to decide the most important regions to which treatment should be applied, it is necessary to know the most frequent sites for secondary deposits. These are, of course, most commonly found in the lumbar glands on the same side. In my opinion these glands should be irradiated in every case, and it has been my practice for some years to include in every case the pelvis, groins, and homolateral lumbar glands, the fields for the latter being extended somewhat across the middle line so as to include the central aortic glands at the same time. This treatment is carried out in two parts, the pelvis being irradiated first, and the lumbar glands subsequently, with or without an interval, according to the general condition of the patient. About three weeks are required for the completion of each part of the irradiation, the total treatment thus extending over a period of not less than six weeks. The treatment is applied daily as is customary nowadays in the treatment of most forms of malignant disease.

As regards the results in these " prophylactic " cases, our series is again very small, but the results are not unsatisfactory.

" Prophylactic " Post-operative Irradiation.

Year	Number treated	Alive Sept. 1938	Dead
1929	1	1	0
1930	0	—	—
1931	0	—	—
1932	4	2	2
1933	1	1	0
1934	3	1	2
	9	5	4

Survival for five years and over : Five out of six ; of these four are still living.

It will be seen from the table that of nine cases treated prophylactically after operation from 1929–35, five remain alive and well. Hinman collected 258 cases treated by orchidectomy without irradiation in various American clinics and found that only 17, or 6½%, lived five years.

We next have to consider whether any improvement could be effected in the results by extending the scope of the irradiation. At least two of the cases who died in our small prophylactic series died with signs of mediastinal deposits. Could the lives of these patients have been prolonged, had they had radiation treatment applied to the mediastinal glands in the first instance ? I think it likely that there might be some improvement in the results by extending the treatment in this way, but the disadvantage is that we should still further prolong an already long treatment, in addition to making much heavier demands on the general condition of the patient. After such extended treatment, it is not likely that a patient would be able to return to full work in less than three to four months from the commencement of the treatment, and I have so far not had the courage to attempt to impose the additional burden.

I think I have said enough to indicate that this question of the scope of the irradiation involves some difficult problems, and I know that radiotherapists would appreciate the advice of surgeons and pathologists on these. An analysis of the sites of metastases in order of frequency would afford some guidance. I would like to emphasize the importance of including a statement of this factor in reported accounts of isolated cases or series of cases. The mere statement that the patient has had

X-ray treatment is of very little value, but the additional information of the regions irradiated and the X-ray dosage would enable us to classify the cases from this point of view so that we should in due course be able to extract the information we require.

We now turn to the consideration of the treatment of the metastatic cases. In my opinion there are few cases in which it is not worth while making the clinical test of exposing an accessible area of disease to two or three test doses in order to form an estimate of the sensitivity of the growth. If the disease should prove to be radiosensitive, the prospect of relief afforded by irradiation is so great that it is unjustifiable to deny the patient this treatment. I have already shown that five of our small series of 18 cases treated between 1930 and 1935 were alive in September of this year. This is not a very high percentage, but having regard to the fact that every one of these cases had metastatic disease, the figure is not unsatisfactory. Most of these cases have been treated by one or other modification of the X-ray bath method developed at St. Bartholomew's Hospital. By means of this method it is possible to expose very large regions, or even the whole trunk, to doses of X-rays which are not very much smaller than those applied to localized lesions.

There is one note of warning that may be sounded in connexion with the treatment of these cases with extensive disease. I have already referred to the fact that toxic symptoms may result from the absorption of the breakdown products of very sensitive growths. In some cases disintegration of the growth is so rapid under X-ray treatment that these toxic signs may be quite severe and even dangerous. For this reason care should always be taken at the commencement of an irradiation for a testicular growth. Only small doses should be applied for the first few days, and the temperature chart carefully watched. If no pyrexia or toxic signs are observed, dosage may be cautiously increased until the patient is having the normal daily amount.

As for the type of radiation, I have no hesitation in saying that this is a disease, in the treatment of which there is no choice of method. X-rays and not radium should be used. The treatment of these growths by interstitial radium is quite wrong, and in fact thoroughly bad, while the treatment of lumbar deposits by moulded apparatus is almost as bad. I have only recently seen a case in which the patient's chances of prolongation of life were forfeited by attempts at treatment of a mass in the lumbar region by radium on moulded apparatus, which resulted in such damage to the skin that the possibility of X-ray treatment could not be entertained. A better case might be made out for the use of the radium bomb, but in depth efficiency and from every other technical point of view, this method is a bad second to X-ray treatment.

This paper gives a report on 27 cases of malignant disease of the testis, 18 metastatic and nine prophylactic, treated by deep X-rays at St. Bartholomew's Hospital between 1929 and 1935. With the exception of one patient who had co-existing lymphadenoma from which he died, and who has not been included, these were all the cases in those years. Ten of the 27 cases are at present alive and well, nine being without signs of the disease. This is a result which could only be expected in this and one or two other varieties of malignant disease, and it is of interest to inquire why the prognosis in malignant disease of the testis, even in the presence of metastases, is so much better than in most other forms of disease. The answer is that most of these growths are so extremely radiosensitive that sufficiently high dosage to cause their destruction can be applied to extensive regions of the body. This answer may seem so self-evident to some that it scarcely needs emphasizing. Yet the fact that the prognosis in this disease is so much better than in most other forms of the disease is not anything like as widely realized as it should be. Quite frequently I am asked to see cases that have been neglected simply because it has been assumed that their secondary deposits make their disease quite hopeless. If this discussion has succeeded in driving home the fact that even advanced cases *are* often treatable, then it will have achieved a great thing.

I will conclude by summarizing the views I have put forward for the treatment of malignant disease of the testis :—

(1) The primary growth should always be removed.

(2) The operation should always be followed by X-ray treatment to the pelvis and groins and to the homolateral lumbar glands. It is possible that the results might be still further improved by irradiation of other regions, but this is a matter which cannot be decided at present.

(3) Secondary deposits, when limited to the lumbar regions, should always be treated.

(4) In cases with multiple secondary deposits, steps should be taken to ascertain the radiosensitivity of the disease with test doses of X-rays. Where there are superficial glands this is easy, but where there are not, it may be necessary to irradiate a section of the deeply-lying disease. Radiosensitive cases should be treated by one or other modification of the " bath " method.

(5) Radium should not be used in the treatment of malignant disease of the testis.

I wish to acknowledge my indebtedness to the members of the staff of St. Bartholomew's Hospital, who have so kindly allowed me to refer to their cases in this communication, and to Mr. Ralph Phillips, Halley Stewart Fellow in Radiotherapy at St. Bartholomew's Hospital, who has collected the cases and followed them up.

Mr. Reginald T. Payne: *Introduction.*—My attention was first directed to this subject many years ago by a teacher who, picturesquely rather than accurately, compared the growth of testicular tumours with that of mushrooms in the night. This description may be true of the " hurricane " type of tumour, but it is certainly not true of the majority of cases. Since then, my attention has been further focused by the almost abysmal gloom which surrounds the subject. It will be part of my contribution this evening to ask the question whether this is entirely justified, or whether it is not rather exaggerated. This gloom pervades current textbooks and teaching, and one of the standard works summarizes the position as follows : " Prognosis is always grave, the majority of cases dying from metastases, often cerebral, about a year from the onset of the tumour."

Is this gloom entirely justified by the facts ? It certainly exists and it has diverse causes, some real, others rather imaginary. Possibly we are more impressed by the dramatic case in which the disease spreads like wildfire than by the cured case which leaves the district and is heard of no more.

Let us look at the question from another point of view. I have been in the habit of asking students which they would select if they had to choose between cancer of the stomach and a growth of the testicle. Without exception, they always choose cancer of the stomach. Do the relative prognostics justify such a choice, or is the choice merely an expression of an ingrained habit of thought ? I recently analysed the data from a series of 506 cases of cancer of the stomach. Out of each 100 cases, only 10 were subjected to radical surgery in the form of one or other type of gastrectomy. Of the patients operated on, three died as the result of operation, leaving seven out of each hundred to form the basis of all the potential cures. It was not possible to follow up all these cases, but the evidence did not suggest that more than one was alive out of each group of a hundred cases at the end of the five-year period. Is the prognosis of malignant disease of the testis worse than this ?

Results of follow-up.—In April 1937 I followed up all the cases of malignant disease of the testis operated on at St. Bartholomew's Hospital during the years 1920–33, and the more recent ones of these have been again followed up to October 1938. In all cases the diagnosis was confirmed pathologically, and only one case during the period has been excluded from the series on the grounds of the absence of adequate pathological data. The orchidectomy was a local operation, and no case was subjected to radical operation. In addition to the orchidectomy, other treatment was carried

out in some of the patients including the excision of inguinal glands, the insertion of radon to abdominal glands, and the use of X-rays. (Some of the data relating to these cases appeared in the *Lancet*, February 12, 1938, p. 364.)

TABLE I.—SUMMARY OF RESULTS

DEATHS.	From operation	2		
	From disease	14	=	16
NOT TRACED				4
CURES.	Five years and over			18
Total				38

Deaths from operation.—Of the 38 cases two died as the result of operation. Case 6 died after seven days. The cause of death was uncertain, and was probably a low grade bronchopneumonia, but no post-mortem was held. Case 25 died twelve days after operation as the result of gas gangrene due to the ulcerated condition of the scrotal skin at time of operation.

Deaths from disease.—Fourteen cases out of the 38 died within the five-year period as the result of the disease, or their deaths were presumed to be due to disease.

There was evidence of metastases at the time of the orchidectomy in three cases (1, 19, and 34).

Ten cases in this group died within the two-year period, whilst three are known to have lived for periods varying from two years ten months to four years one month. The latter patient had metastases in the inguinal glands at the time of operation, and was treated by X-rays subsequently, but at no stage was free from disease.

Cures, five years and over.—Eighteen of the 38 cases survived the five-year period, giving a cure rate of 47·3%. Thirteen of these patients are still alive and well. Case 3 has not been traced since 1932, but had then survived a period of eleven years. Cases 8 and 11 died from unknown causes at periods of ten years and nine years two months respectively. Case 9 was in good health for eight years and then developed a teratoma of the opposite testicle and now has abdominal secondaries. Case 35 remained free from disease for five years four months and then developed secondary deposits in the neck and other sites.

TABLE II.—FIVE-YEAR CURES

Case		
3	11 years	Not traced since 1932
7	13 years 4 months	Alive and well 14.4.37
8	10 years	Died 1934, cause unknown
9	8 years	Then teratoma opposite testis ; now abdominal
10	12 years 1 month	Alive and well 30.4.37 [secondaries
11	9 years 2 months	Died 3.34, cause unknown
12	11 years	Alive and well 13.4.37
14	10 years 10 months	Alive and well April 1937
17	16 years	Alive and well 19.4.37
18	8 years 7 months	Alive and well 15.4.37
20	8 years 10 months	Alive and well 26.4.37
21	8 years 11 months	Alive and well 15.4.37
22	6 years 6 months	Alive and well 15.4.37
26	6 years 8 months	Alive and well 15.4.37
29	7 years 11 months	Alive and well 7.10.38
31	5 years 6 months	Alive and well 15.4.37
32	5 years 11 months	Alive and well 4.10.38
35	6 years 1 month	Death from suicide 1.9.38. For 5 years 4 months was completely free from disease

Alive and well	13
Untraced since 1932 (3)	1
Died, cause unknown (8, 11)	2
Teratoma opposite testis (9)	1
Death from secondaries after 6 years 1 month (35)	1
Total	18

Histological data.—In all the cases investigated, histological data were available. There were 19 teratomas and 19 seminomas. Under the heading "teratoma" have been included all the tumours having a definitely mixed structure. On the other hand, under the heading of "seminoma" have been included not only the tumours of this type, but also those described in the earlier case records as alveolar sarcomas. There were no chorion-epitheliomata in the series. Of the cases coming into the five-year cure group, nine were teratomas and nine were seminomas.

TABLE III.

Teratomas	19
Seminomas	19
Five-Year Cures.	
Teratomas	9
Seminomas	9

With increasing correlation of histology, biological tests, and response to irradiation, it may be possible to arrive at a more accurate classification of these tumours. But at the present time, little would seem to be gained by any subdivision beyond the three main groups of teratoma, seminoma, and chorion-epithelioma. It has been suggested that if more sections were taken from these cases a larger proportion of cases would prove to be teratomas and not seminomas. This may explain some of the cases of radio-resistant seminomas.

Duration of symptoms.—The average duration of symptoms before operation was as follows :—

TABLE IV.

	Number of cases	Average duration
Whole group ..	38	7·5 months
Five-year cure ..	18	6·9 months
Dying from disease	14	8·7 months

The average of 7·5 months, in the whole group, is a surprisingly long period, and one that it should be possible to reduce considerably. It will be seen that the time difference between the five-year cure group and the cases dying from disease was approximately seven weeks. This fact in itself suggests that the type of the disease is of outstanding importance.

Irradiation.—Of the 38 patients, 15 were treated by means of some form of irradiation in addition to orchidectomy. This included X-rays, deep X-rays, and the use of radon in one patient (Case 19). The X-rays were employed in some cases therapeutically and in others prophylactically (so-called). Fairly high voltages were used, but Case 32 (1932) was the first one of the series to be treated with deep X-rays.

In the 14 cases dying from the disease, eight had been irradiated, one of these being treated by radon. Amongst these the longest survival was Case 1, who lived four years one month. At the time of operation the inguinal glands were also involved and were excised. Subsequent to this he was never free from disease.

In the 18 patients in the five-year cure group, irradiation was used in seven (Cases 8, 11, 18, 22, 29, 32, and 35). Case 11 (seminoma) had an abdominal recurrence eight months after operation, which was proved by section to be a seminoma. This patient remained well for nine years two months after operation, and then died from an unknown cause. In the other six cases there was no definite evidence of metastases at the time of irradiation, but Case 35, after five years and four months' complete freedom from symptoms, developed metastases and died nine months later.

Diagnosis.—Mistakes still occur in the diagnosis of testicular swellings, and some are almost unavoidable. The most frequent mistake is the removal of a gummatous testis for a neoplastic one. Of much greater importance is the failure to recognize

the presence of a testicular tumour. In the series quoted, delay in carrying out orchidectomy was in a few cases due to repeated tappings, to a radical cure of a supposed idiopathic hydrocele, and to the failure to recognize the real cause of a hæmatocele. The extended use of the Aschheim-Zondek test should be of great value in the diagnosis of testicular tumours and of recurrences, provided that the quantitative test be employed. The highest figures for prolan A excretion are found in cases of chorion-epithelioma, the lowest figures in cases of teratoma, whilst the seminomas occupy an intermediate position. At the same time the therapeutic response to irradiation is closely linked with prolan A excretion. American workers have paid particular attention to these biological tests, but as yet there has been no confirmation in this country in any large series of cases.

Conclusions.—Recent advances have made the diagnosis of testicular tumours more certain and their treatment more efficient.

On the diagnostic side, some clinical mistakes must inevitably occur and lead either to delay or to an unnecessary orchidectomy, but the increasing use of biological tests should reduce the size of this group.

On the therapeutic side, the subject is only just emerging from a transitional phase. Two facts, however, are important: firstly that surgery will cure a small but uncertain number of cases, and secondly that irradiation will control and even cure metastatic deposits. I do not feel, however, that deep X-ray treatment alone should be employed when orchidectomy is possible. The local operation is simple and safe, and personally I believe a summation of effects from a combination of operation and irradiation is likely to give the best results. The very late recurrences which sometimes occur are disconcerting, but they can be recognized by regular clinical and biological tests, and for this an adequate follow-up is essential. At the present time I do not think there is any place for the radical operation.

Prognosis in malignant disease of the testis may be bad, but it is not hopeless, and we have now newer and more valuable diagnostic and therapeutic agents at hand to assist us. We shall do little to dispel the gloom that surrounds this subject unless we adjust our attitude in these respects.

[*December* 7, 1938]

DISCUSSION ON THE DIAGNOSIS AND TREATMENT OF ACUTE PANCREATITIS

Mr. John Morley: It is a remarkable fact that the disease we are to consider this evening has never before been a subject of discussion by this Section since the Royal Society of Medicine was incorporated in 1907. Acute hæmorrhagic pancreatitis is a comparatively rare disease, and no one surgeon is likely to have had an impressively large personal experience of it. But with all its rarity it presents many difficult problems in ætiology, diagnosis, and treatment.

Although this discussion is limited to the diagnosis and treatment of acute pancreatitis, one cannot avoid a preliminary survey of the question of pathogenesis—a subject so involved that most of the experimental and clinical work dealing with the disease has been chiefly concerned with it.

The most arresting fact in the pathology of the disease is its very frequent association with gall-stones. Egdahl (1907) found that 42% of his cases were associated with gall-stones, and von Schmieden and Sebening (1927) in 1,278 collected cases found that 69·8% had gall-stones. In a series of 17 cases under my care gall-stones were found in 11 or 64·7%.

Opie, in 1901, described a case in which a small stone impacted in the ampulla of Vater caused a reflux of bile into the duct of Wirsung, and he advanced the theory that this conversion of the bile duct and the pancreatic duct into a common channel was the usual method by which the disease was brought about. His experimental production of acute hæmorrhagic pancreatitis in dogs by injection of bile into the main pancreatic duct appeared at first to provide striking confirmation of this theory. Anatomical investigations into the variable arrangement of the terminations of the bile duct and the duct of Wirsung in man provided, however, conflicting results. Mann and Giordano (1923) found that in only 3·5% of subjects did the anatomical arrangement of the ducts permit the formation of a common channel by obstruction at the papilla. Cameron and Noble (1924), on the other hand, came to the conclusion that in 75% of individuals a calculus impacted at the papilla could produce a common channel. However this may be, it is quite plain from operative and post-mortem findings that in actual cases of the disease the impaction of a stone in the ampulla is a rare event. Thus in only 4·5% of von Schmieden and Sebening's 1,278 collected cases was a stone present in the ampulla. It has often been pointed out that a stone impacted in the ampulla is quite as likely to cause obstruction of the pancreatic duct as to give rise to a reflux of bile into it.

Archibald (1919) suggested that a spasm of the sphincter of Oddi in the absence of a stone might make a continuous channel and allow a reflux of bile into the pancreas. But Mann and Giordano found cogent anatomical reasons against this theory. It has been established that by the injection not only of bile but of a large variety of other irritating fluids into the pancreatic duct, acute hæmorrhagic pancreatitis can readily be produced (Dragstedt, Haymond and Ellis, 1934). Rich and Duff (1936) have pointed out that the typical lesion is not produced unless the volume of fluid injected is considerable and is bulky enough to cause rupture of the pancreatic acini. They conclude that the escape of trypsin into the interstitial tissue of the pancreas is the essential causative factor.

Since trypsinogen is normally secreted in an inactive form and is only converted into trypsin by the enterokinase of the intestine, we have to account for the activation of the trypsin inside the pancreas in pancreatitis, for there is no evidence that enterokinase gains access to the interior of the pancreatic duct. Pure bile appears to be incapable of activating trypsinogen, but it has been proved by various investigators that bile infected by bacteria may do it. It has also been suggested that pure pancreatic juice may, after a rich protein meal, show proteolytic activity within the ducts in the absence of infection, or that when forced by obstruction of the ducts outside the acinar system it may be activated by contact with the tissue fluids.

Summarizing a large body of evidence we may conclude that in some 60% of cases, where gall-stones or other disease of the biliary tract is present, reflux of bile or infection or obstruction of the pancreatic duct may be responsible for the escape of active trypsin into the interstitial tissue of the pancreas. Such rare causes of duct obstruction and infection as the intrusion of a round worm or the pressure of a duodenal diverticulum need not concern us here, nor shall I consider the blood-borne infection by which the pancreas is occasionally affected in mumps. There remain some 40% of cases in which there is evidence neither of gall-stones nor of infection. How are we to account for the disease in this large proportion of cases? Rich and Duff (1936) have drawn attention to a peculiar hyaline necrosis of the walls of the pancreatic arteries and veins in this disease. They provide convincing evidence that this necrosis is the initial lesion giving rise to the interstitial hæmorrhage, and that it is due to the action of active trypsin that has escaped from the acinar system under pressure. They have produced the same vascular necrosis and resulting hæmorrhage in the subcutaneous tissue of dogs by injecting active trypsin. Bile similarly injected gave negative results.

Addressing themselves to the problem how this escape of trypsin may be accounted

for in the absence of causes external to the pancreas such as gall-stones, they have drawn attention to a remarkable proliferative metaplasia of the pancreatic duct epithelium that occurs in a large number of cases. In a series of 150 autopsies in subjects over 25 years of age they found this duct metaplasia of the pancreas in 18·6%. Priesel (1922) had previously described the proliferative change in the ducts, chiefly in elderly people, and found it present in some 10% of glands examined but did not relate it to hæmorrhagic pancreatitis.

In a series of 24 cases of acute pancreatitis Rich and Duff found this metaplasia in no less than 13. They suggest that the obstruction to the ducts caused by this proliferation may be responsible for the escape of trypsin into the interstitial tissue of the gland, and so account for the hæmorrhagic pancreatitis in some cases in which extrinsic causes of duct obstruction or infection are lacking. They also draw attention to inspissated secretion sometimes seen in the pancreatic ducts which appears to be another cause of their obstruction.

By the kindness of my colleague, Dr. W. Susman, I show (figs. 1, 2, and 3) an illustration of this proliferative metaplasia, the cause of which is quite obscure, and also examples of inspissated secretion within the ducts, and heterotopic rests under the duct epithelium. Further pathological investigations on the subject are needed, but here we may have the key to a mystery that has long baffled the pathologist, viz. how to account for acute hæmorrhagic pancreatitis that arises in the absence of gall-stones or obstruction at Vater's ampulla, or primary infection.

Diagnosis.—Although the difficulty in diagnosing this disease is emphasized in most of the clinical descriptions in the literature, I believe it to be true, as Moynihan (1925) pointed out, that few clinical pictures are clearer than that shown by the more severe cases of this malady. The patient is usually florid and elderly, with a high blood-pressure and perhaps a taste for alcohol and good living. The attack starts, often soon after a full meal, with the sudden onset—hardly less sudden than in a perforated ulcer—of an epigastric pain of savage intensity. The pain bores its way through to the back and rapidly becomes an extreme agony. It is singularly resistant to morphia. The pain of a perforated ulcer or an acute obstructive cholecystitis may be fatally masked by a dose of morphia, but seldom that of acute hæmorrhagic pancreatitis. We find tenderness and some rigidity extending right across the upper abdomen, but not the board-like rigidity of a perforated ulcer. Remarkably early in the attack the transverse colon becomes paralysed and distended with gas, so that we find early upper abdominal distension.

The early circulatory depression alone is almost diagnostic of the disease in a severe case. While in a perforated ulcer the pulse in the early hours after the catastrophe is slow and full, in acute hæmorrhagic pancreatitis the pulse is alarmingly rapid and poor in quality from the first. The temperature is subnormal in this early stage. With this circulatory failure we find the most significant sign, cyanosis of the lips and ears and sometimes a peculiar bluish mottling of the abdominal wall as well. Halsted (1901) described the white imprint left by his fingers after palpating the cyanosed abdominal skin. There is almost invariably vomiting which may be urgent and persistent, and the respirations are both rapid and shallow. It is the combination of an extremity of agonizing pain so severe that the patient feels like dying, collapse of the pulse and cyanosis that makes the clinical picture so distinctive. A rare sign described by Grey Turner in cases that survived a few days is a patch of brownish discoloration in either flank or in the umbilical region.

Though an acute diffuse hæmorrhagic pancreatitis can hardly fail to be recognized by a surgeon who bears it in mind as a possibility, we must remember that the disease occurs in varying degrees of severity, and it is with the milder forms that difficulty in diagnosis may arise. In these the inflammatory lesion may be limited to a portion of the gland, most commonly the head, but sometimes only the tail ; or there may be a diffuse swelling of the pancreas with fat necrosis scattered through the omenta, but

with little or no interstitial hæmorrhage, no blood-stained fluid in the peritoneal cavity, and no massive necrosis of the gland.

It is noteworthy that in many of the milder cases there is a history of previous recurrent attacks, and though the interpretation of these is uncertain in view of the frequent presence of gall-stones, there is often good evidence at operation, from

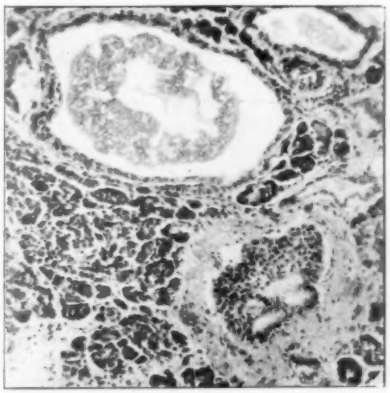

FIG. 1.—Shows proliferative metaplasia in a small duct and inspissated secretion with commencing metaplasia in a larger one. (Section lent by Dr. W. Susman.)

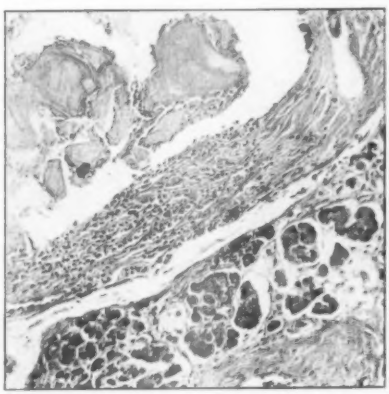

FIG. 2.

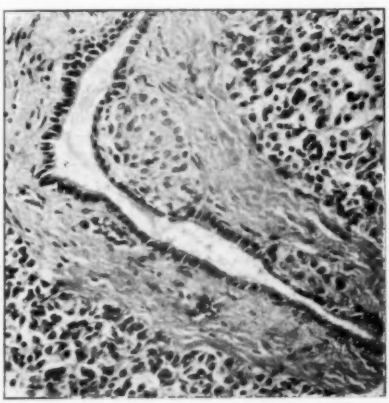

FIG. 3.

FIG. 2.—Inspissated secretion in a large duct, with destruction of living epithelium and leucocytic infiltration of the duct well. (Section lent by Dr. W. Susman.)

FIG. 3.—Heterotopic rests under duct epithelium. (Section lent by Dr. W. Susman.)

scarring and localized induration of the pancreas, that earlier attacks of focal acute pancreatitis have occurred.

The differential diagnosis in these milder cases is difficult because of the absence of the rapid, failing pulse and the cyanosis. Without these distinctive features, the

case may be taken for high intestinal obstruction, perforated gastric or duodenal ulcer, acute obstructive cholecystitis, spontaneous rupture of the common bile duct, or mesenteric thrombosis.

In *high intestinal obstruction* the vomiting is even more urgent than in acute pancreatitis, and soon becomes copious and effortless. The bilious vomit gives place at the same time to typical small-intestine contents. The pain, in many cases of intestinal obstruction, although continuous, has an intermittent or spasmodic element in it that is not found in acute pancreatitis, and it is rarely felt in the back.

In *perforated ulcer of the stomach* there is usually a history of epigastric pain with the characteristic relation to food. This history is long and periodic in the case of a chronic ulcer, or limited, in the acute ulcer, to the few days before the perforation. Shoulder-tip pain from phrenic nerve irritation is common in perforated ulcer, less common in pancreatitis. Early distension of the upper abdomen occurs with pancreatitis rather than with perforated ulcer, and both tenderness and rigidity are more extreme in perforated ulcer.

Acute obstructive cholecystitis may closely simulate an acute inflammation limited to the head of the pancreas. An earlier rise of temperature than in acute pancreatitis, and more extreme tenderness and rigidity are usually to be observed. The tenderness and rigidity may be noticed to extend gradually lower down on the right of the abdomen as the gall-bladder becomes progressively more distended.

Spontaneous rupture of the common bile duct, due as a rule to the ulceration through its wall of a gall-stone, is a rare condition of which I have observed only two cases. There is an extensive infiltration of bile between the layers of the lesser omentum, along the greater curvature of the stomach, into the base of the transverse mesocolon and around the pancreas. Great pain and considerable circulatory depression are caused, and I know of no clinical features by which it can be differentiated from acute pancreatitis.

Thrombosis and embolism of the superior mesenteric artery may also be exceedingly difficult to diagnose from acute pancreatitis in the early stage. The tenderness and tumidity are, however, situated rather in the central than the upper abdomen, and if the patient survives long enough for melæna to occur the diagnosis becomes clear.

In rare cases *coronary thrombosis* may cause both cyanosis and epigastric pain, but the cyanosis is more extreme than in pancreatitis and the pain is substernal rather than over the pancreas as a rule.

Laboratory aids to diagnosis.—In view of all these difficulties in diagnosis, it is natural that we should turn to the clinical pathologist for help. The time-honoured test associated with the name of Loewi, that consists in instilling two drops of 1 : 1,000 adrenaline into the conjunctival sac, may, I think, be dismissed as useless. Dilatation of the pupil from adrenaline is inconstant in patients with proved pancreatitis, and may occur in patients who are not suffering from pancreatitis.

In the estimation of diastase (or amylase) in the urine we have, however, a laboratory test of proved value. The diastatic index is defined as the number of c.c. of 0·1% starch digested by 1 c.c. of urine in thirty minutes at 37–38° C. Whereas the normal diastatic index ranges from 4 to 50, in acute pancreatitis it varies from 100 to 2,000, and this striking rise appears early, though I cannot ascertain how early, in the disease. No other laboratory test compares with it in importance. Estimation of blood-diastase has its advocates, but is technically more difficult to carry out than that of urinary diastase.

Slight glycosuria may occur, and also a slightly raised blood-sugar, but these are not constant. Tests for pancreatic efficiency such as the estimation of fat in the fæces are only of value in cases of chronic pancreatitis and carcinoma of the pancreas.

Mortality and treatment.—The mortality of this disease is a high one, ranging from 30–60% or even higher in various series of collected cases. In my own series of 17 cases proved by operation it was 35·3%, but some cases were relatively mild (Table I).

It is probable that it will always be high, since the most acute form of pancreatitis is hardly compatible with life. It is well known that patients sometimes die outright from the shock associated with the initial hæmorrhage. Others survive that shock, only to succumb to profound toxæmia due to absorption of the products of protein-splitting in and around the pancreas, to intestinal paralysis, or to the exhaustion resulting from a secondary septic infection of the necrosed gland.

TABLE I

		Died
Cases of acute pancreatitis ..	17	6 = 35·3%
Gall-stones present (2 in ampulla)	11	
Gross hæmorrhage in pancreas ..	11	
Fat necrosis	13	
Simple swelling of pancreas (mumps)	1	

The writers on this subject of ten or twenty years ago plead for early operation with the same insistence with which we urge early intervention in acute intestinal obstruction or perforated duodenal ulcer. They plainly entertained no doubts at all on the matter, but we may well adopt a more critical attitude of mind and ask ourselves whether some of our cases may not have recovered in spite of our active surgical efforts, and whether others may not have had the fatal issue ensured by a too-precipitate operation.

As long as acute pancreatitis was regarded as undiagnosable save by a lucky guess, there was an unanswerable argument for an early diagnostic incision, for otherwise we might let a perforated ulcer cause a fatal peritonitis, or allow a strangulated coil of gut to go on to gangrene. I am far from suggesting that exploration for diagnostic purposes is entirely outmoded in this disease, but the necessity for it grows steadily less with the increase of our knowledge. We must ask ourselves what, apart from diagnosis, we can achieve by early operation (Table II).

TABLE II.—OPERATIVE PROCEDURES IN 17 CASES

		Died
Simple drain to pancreas	8	3
Cholecystostomy and drain	4	1
Chelecystostomy, choledochotomy, and drain	3	2
Choledochotomy and drain	1	0
Cholecystectomy and drain	1	0
Laparotomy (mumps)	1	0

Plainly we cannot undo the damage already done by the escaped trypsin and lipase. But many surgeons have stressed the importance of drainage. Mr. T. B. Mouat of Sheffield, in a personal communication has told me of a series of seven cases, not of the most fulminating type, in which he performed posterior drainage of the head of the pancreas by mobilizing the second part of the duodenum, and also drained the gall-bladder. All seven cases recovered. Some authorities advocate drainage of the peritoneum, both the lesser sac and the greater sac below the transverse colon, with the idea that the blood-stained peritoneal exudate is a chief source of toxic absorption. I know of no convincing evidence that this is so, and I regard the necrotic gland itself as the main source of the overwhelming toxæmia by reason of the poisonous products of the proteolytic activity of the extravasated trypsin. The pathological evidence appears to me to be against bacterial invasion of the gland as the prime cause of the disease or as the source of the early toxæmia. Invasion by septic organisms is, I suggest, secondary to the massive necrosis ; not the relatively unimportant fat necrosis but the gangrene of the whole or a portion of the gland. I submit

that we can no more drain the necrosed pancreas effectively, so as to prevent toxic absorption, than we can drain a carbuncle before suppuration has occurred.

I have grown equally sceptical as to the value of early drainage of the gall-bladder or common bile duct. We have seen that impaction of a gall-stone in Vater's ampulla is a pathological rarity, and even if we accept the common channel theory for the majority of cases, the harm is done by the time symptoms arise, and early drainage of the biliary system is like locking the stable door after the horse has been stolen.

Some recent statistics by Walzel (1934) provide a strong argument against the efficacy of early intervention. He collected 30 cases from the years 1926–28 in which early operation was carried out with a mortality of 86·67%, and contrasted them with a series of 46 cases from 1929 to 1934, in which later intervention only was employed with a mortality of 28·26%.

The conclusions I would suggest are these: In early cases where the diagnosis is clear treatment should be non-operative, and should consist of intravenous saline infusion to combat the circulatory collapse and toxæmia, with continuous gastric drainage by a Ryle's tube wherever vomiting is severe. Rich and Duff have drawn attention to the case of a girl of 13 suffering from burns who was given a large amount of glucose intravenously. She died of acute hæmorrhagic pancreatitis twelve hours after the glucose infusion was begun. They quote Babkin's (1935) experimental finding that elevation of the blood-sugar causes an increased flow of pancreatic juice rich in ferments, and suggest that intravenous glucose may be dangerous in the treatment of acute pancreatitis. Whenever diagnosis is considered uncertain early laparotomy must be done, but the discovery of fat necrosis and a swollen hæmorrhagic pancreas should be the signal for a rapid retreat. Most surgeons will prefer to leave a drainage tube down to the gland for a few days, since if it does no great good it cannot do much harm. The main indication for operation in cases that survive the first few days will be abscess formation, as shown by a rising temperature, leucocytosis, and local swelling. Later still, if the acute symptoms have subsided, the biliary tract should be explored for gall-stones to prevent a further attack. If this line of approach is criticized as too timid, I would urge that it is more likely to give us a lower mortality than the more drastic methods of the past.

But surely it is equally important to think of the prevention of this disease. No matter what view we take of the manner in which gall-stones predispose to acute pancreatitis we cannot help believing that they do cause it. I have mentioned that in my own series of 17 cases operated on 11, or 64·7%, had gall-stones. Many other similar series could be quoted. Every successful operation for gall-stones saves the patient from a possible acute pancreatitis. I believe there is in many quarters far too much readiness to palter with the so-called medical treatment of gall-stones. To treat gall-stones medically when there is no real contra-indication to operation is no more efficacious than the medical treatment of stone in the urinary bladder.

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Mr. H. Blacow Yates: The dramatic onset and varied manifestations of this disease have held the interest of the profession for years, resulting in a well-known and characteristic clinical picture. A correct diagnosis should be possible, and in a review of the cases available to me, I have found that this has been so. The cardinal symptoms are so definite that a careful search for the associated signs will rarely fail to allay any doubt.

The satisfaction derived from our greater ability to diagnose the malady is offset by our uncertainty in regard to treatment. It is not easy to assess exactly the true values of the opposed methods. It is regrettable that no helpful observations on the conservative treatment of acute pancreatitis have come from British surgeons or physicians.

Either the disease is more frequently diagnosed now or its incidence is slightly on the increase. Digby Chamberlain [1] gave the incidence for the first decade after the War as 1 : 5,000 admissions to the Leeds General Infirmary. The Sheffield figures available show that in the past decade acute pancreatitis has been encountered more frequently. Even then it is an uncommon disease. The average age in men seems to be 60, but much less in women, who are more prone to the disease. They are frequently attacked before the age of 30, and at the moment I have in hospital an undoubted case in a girl of 19. The association between this disease and some pre-existing pathological condition of the biliary tract would appear to be generally established. The histories frequently reveal flatulent dyspepsia and attacks of upper abdominal pain. During the last twenty years the surgical treatment of chronic gall-bladder infection has been more intense and drastic than formerly, and it must be admitted that the routine substitution of cholecystectomy for cholecystostomy has failed to diminish the incidence of acute pancreatitis. If the pathogenesis of pancreatitis were concerned with infection within the gall-bladder wall, we had a right to expect a different result.

As for symptoms, intense pain in the epigastrium and often in the hypochondria, back and left shoulder, seems universal. Vomiting is frequent and persistent. The temperature is normal or subnormal, and pulse usually rapid. The respirations may be quick and shallow and some cyanosis is frequent. Detectable bile in the urine and visible jaundice in my experience are common, roughly in one-third of the cases. Later, when the abdomen distends, the epigastric tenderness spreads to the flanks and lower abdomen, but rigidity is never marked. Costovertebral tenderness is a most important sign more often present than absent. Shock is usually considerable at first, and in some cases extreme. In one case seen two years ago it was impossible to move the patient from her home in the country into a nursing home until the fourth day of the disease.

Of laboratory tests, I shall be surprised if anyone denies the value of the urinary diastase estimation. Its importance has grown with the regression of diagnostic laparotomy. I have found it usually increased and frequently excessively so. In the girl of 19 under treatment at present the figure was over 300. In cases where a normal figure is found in the earliest stages, an increased index will usually be present later. Hyperglycæmia is at times found, but American authorities stress its prognostic rather than its diagnostic importance. If it persists the prognosis is bad. Serum lipase is said to be increased in this disease but I have no personal experience of the test. I have never found the adrenaline mydriatic test reliable.

Two conditions are most frequently cited as likely to be confused with acute pancreatitis, acute intestinal obstruction and perforation of a peptic ulcer. I maintain that the differentiating signs and symptoms are such that this mistake ought seldom to arise.

A disease which may most closely mimic acute pancreatitis is acute pericarditis with effusion. The onset here is sudden and distinction between the two may be difficult, especially if the case is not seen until the disease has been present three or

four days. A case which I saw nearly twenty years ago impressed me. A man had been seized with sudden severe pain in the left lower chest, epigastrium and back, some four days before. He was orthopnœic, cyanosed, and extremely tender in the upper abdomen, which was somewhat distended. Vomiting had been present and the bowels confined since onset of the illness. His pulse was very rapid and thin, and exhibited the variation typical of pulsus parodoxicus. Before this was detected operation had been contemplated under the impression that the man was suffering from pancreatic necrosis. Attention was directed to the heart and the compression of the left lung base gave rise to the tubular breathing pointed out by Bamberger. A radiogram showed an enormous cardiac shadow and a certain fatality under anæsthesia was avoided.

We must consider and exclude both pericardial and coronary disease in all cases of suspected pancreatitis. It may not be easy. Being warned by the significance of the above case I have paid special attention to the heart and the left lung base. Often we find dullness here with diminished or even absent breath sounds. The heart sounds in acute pancreatitis are often weak, and we may be very doubtful whether a stoutish patient is suffering from the one disease or the other in the early stages. The most serious surgical error would be to resort to operation in the belief that the epigastric tenderness due to hepatic engorgement, was due to acute pancreatitis.

The ætiology is a matter of uncertainty. Obstruction of the ampulla of Vater by stone, round worm, or duodenal pouch, has been found in acute pancreatitis. I have actually seen three gall-stones post mortem in the pancreatic duct. But calculi are removed almost daily from the ampulla for obstructive jaundice in persons who have not developed pancreatitis. I have not found that stones are located in the common duct at all frequently in acute pancreatitis. When they have been so found they are not often at the ampulla.

Bile injected into the pancreatic duct causes œdema of the gland in cats [2]. Various experiments have been carried out on the sphincter of Oddi also in cats, but can we infer that a similar sphincter functions in man ? The work done by McGowan, Butsch and Walters [3] on the pressure in the common duct of man following cholecystectomy would necessitate the existence of such a sphincter. Certain anatomical variations at the ampulla might conceivably permit of bile being forced into the duct of Wirsung. But reflux of bile cannot explain the case of acute pancreatitis affecting an accessory organ in the wall of the jejunum.

An alternative view that infection spreads from the gall-bladder to the pancreas via the lymphatics seems even less satisfactory. Pancreatitis does not commence with fever or rigors or other common associates of the onset of an acute infective condition.

A further explanation must be sought for cases not associated with biliary lithiasis, and I have for some time been intrigued by the apoplectic theory of the French surgeons. In the summer of 1937 Gregoire, Pierre Duval and Brocq [4] gave most interesting papers to the Fellows of the English Royal College of Surgeons who visited Paris at the invitation of the Academie de Chirurgie. They have shown that the injection of horse serum, for instance, into the pancreatic vein of a sensitized animal, using local anæsthesia, produces acute œdema of the pancreas. Briefly it is suggested that a condition of pancreatic apoplexy is produced and there is developed an extreme vasodilatation of the capillaries of the organ with subsequent hæmorrhage. Gregoire states that visceral apoplexy (intestinal, pancreatic, pulmonary, uterine, and even cerebral) is a " consequence of stasis due to vasodilatation caused by irritation of the vegetative nervous system. The stasis is such as to cause asphyxia of the tissues and total or partial death of the organ involved ". In acute pancreatitis the escape of glandular ferments and steatonecrosis are secondary developments, as is any infection. They insist on the disease being called pancreatic apoplexy or acute pancreatic necrosis rather than by the title by which we know it and which suggests

an inflammatory condition initially. This possible causation of the disease must be kept before us when we endeavour to plan conservative measures.

Many problems require explanation in this disease which I have not the time to mention. I should like to bring forward one point. Occasionally in acute pancreatitis blueness is found around the umbilicus. This has been said to be part of the cyanosis and little attention has been paid to it. I suggest it is due to obstruction of the portal venous radicles. In two cases post-mortem examination revealed thrombosis of the superior mesenteric and splenic veins. I suggest that the blue umbilicus is an attempted collateral circulation due to the above cause, and if this is correct all cases where it is manifest will probably die. The relation of the portal vein to the swollen pancreas is worthy of careful consideration in future. Compression of this vein and not the escape of blood from the pancreatic duct, as I think Upcott suggested, may explain the melæna found at times and may be a factor in the peritoneal effusion. Brocq quotes Gilbert and Chabrol as having shown that " portal hypertension may also, by its interference with the circulation, be a cause of acute necrosis ". If superior and mesenteric venous thrombosis is frequent in acute pancreatic necrosis we should expect the spleen to be enlarged post mortem. I can find no statistics on this point.

Leaving the alluring fields of speculation we come to the more prosaic paths of facts and figures. Surgeons are less inclined to operate on pancreatitis once the diagnosis has been made. In the past the surgical results have been bad. My figures show that 50% of the cases admitted to the surgical wards at the Sheffield Royal Hospital have died either after operation or because they were too ill to be submitted to it. Our feeling of dissatisfaction may have been stimulated by the reports from continental centres of the almost incredible results following purely conservative measures. Fron Denmark we learn that 50 consecutive cases of this disease recovered without operation, while other figures show an 8% to 15% mortality. It will be argued that the diagnosis may have been wrong and that the disease seems more frequent and less virulent than in this country, but even allowing for this, the figures are such that it is inevitable that early operation should be avoided, except in those cases where we are otherwise unable to make a diagnosis with reasonable certainty. There is no call for me to discuss the various types of surgery which have been carried out beyond stating that the best results have followed simple gall-bladder drainage. In the three cases under my review where the gall-bladder was removed, death followed. We should be content to drain the gall-bladder and not attempt the more difficult procedure of drainage of the common duct.

In future I think a middle course will be steered. The initial shock should be countered by morphine. I am aware that morphine raises the tension in the common duct and may be objectionable therefore, but I have found no drug which relieves the agonizing pain other than morphine or one of its derivatives. Atropine has been injected first in the hope that this may prevent the spasm of the sphincter of Oddi caused by morphine. (It is certain that atropine administered following the morphine has no effect. In those cases where vomiting has been troublesome an indwelling duodenal tube and suction have been employed. Hypochloræmia, being a common finding, chlorides must be given by rectal and possibly intravenous routes. Glucose should not be given indiscriminately. Low sugar tolerance and hyperglycæmia may be present and insulin may be necessary.

In the early stages I have given ephedrine with the intention of overcoming the capillary stasis in the pancreas which the French consider the initial change. If this can be overcome there is some hope that necrosis and subsequent infection can be prevented. The German and Scandinavian surgeons use ephetonin [5].

I would reserve surgery for those cases which have recovered and where investigations point to some coexisting pathological lesion of the biliary tract. Minimal surgical measures may still be necessary in the later stages of the disease itself.

(1) In those cases where bile in the urine and jaundice have been found, simple gall-bladder drainage under local anæsthesia should be done if satisfactory progress is not taking place.

(2) Where medical measures have not allayed the necrosis, infection has been added and suppuration is suspected, it would appear that pancreatic drainage must be carried out.

(3) When duodenal suction, repeated enemata, and similar measures, have failed to overcome the intestinal distension and irritative peritonitis, it may be necessary to insert a pelvic drain under local anæsthesia.

Much needs to be done to improve the measures employed in the period of delay. One writer even suggests that the medical treatment should include " glucose with insulin, starvation days, and days with a high carbohydrate diet " [6], surely a grave reflection on the medical régime. But the lack of knowledge here does not mean that we should revert to our previous belligerent measures. Rather does it behove us to be dissatisfied with the results of past surgical efforts. seek the aid of physicians and physiologists, and at least give trial to treatment which, in spite of its shortcomings, appears to hold out greater hope for the future.

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Mr. W. H. Ogilvie: I would thank the openers of this discussion for the admirable manner in which they have presented a difficult subject, but I would join issue with both of them on two points ; they have committed themselves in support of Moynihan's dictum that the pain of pancreatitis is agonizing, and they have advocated the non-operative treatment of pancreatitis. Surgeons are called to acute abdominal emergencies while they are senior residents or junior honoraries, but they are not asked to open discussions till they have reached eminence. They then bring to the task a riper judgment, but a less vivid because less recent experience, and they can be excused if they refresh themselves at the gushing fountain of continental literature. Speaking as one who is still an assistant surgeon, who must still attend emergencies, and who has seen cases of pancreatitis every year for the past twenty years, I am convinced that both of these views are wrong.

If we must grade abdominal pains, the worst is certainly that of duodenal perforation, the next that of gall-stone colic, the third that of renal colic ; fourth, but coming a long way after the first three, and not usually standing out in severity from several other abdominal pains, comes that of acute pancreatitis. The pain in pancreatitis is a " nasty belly ache ", but not an agony. In my opinion it is this moderate severity of the pain, when contrasted with the patently critical condition of the patient and the signs in the abdomen of a general peritonitis, that gives the clinical picture on which we must base the diagnosis. Staining round the umbilicus or in the loin, cyanosis, the colour of the ears—these are fancy trifles that may or may not help, generally not. I have not yet found a resident surgical officer engaged in daily contact with emergency surgery who disagrees with me on this estimate of pancreatic pain.

The statement that cases of acute pancreatitis do better when treated by expectancy than by surgery is as sound as any statement based on statistics alone. It is

based on figures rather than pathology, on the authority of German writers rather than the experience of British surgeons. German surgery is linked to the laboratory and perfected in the operating theatre, but it never approaches the bedside; we have much to learn from them, and if travel and study count for anything we are learning it, but we have also much to teach them in the way of clinical science.

A comparison of two series, one of which contains all the mild cases, the other all the desperate ones, may be amusing, but it cannot make sense. We can thus prove beyond doubt to those for whom statistics are the unerring standard of truth, that transfusion is dangerous since the mortality in transfused patients is higher than in those not transfused, that the oxygen tent is useless in pulmonary disorders, indeed that a hospital is the worst place in which to treat a sick man.

Statistical pancreatitis is pancreatitis diagnosed by the diastase test, and the series includes many mild cases admitted for vague abdominal pain. Without this test they would have been discharged undiagnosed; certified by the biochemist, they become the cures of expectancy. But if we omit these trivial cases that any surgeon with horse sense and a sound clinical training would leave alone, and confine our attention to the genuine acute abdominal emergencies, pathological and surgical principles demand operation, and experience shows that operation gives the only chance. Let us take those patients only who, with a history of six hours or less, have a pulse-rate of 120 or more, a systolic pressure of 100 mm. or under, and all the physical signs of a general peritonitis. They have a pancreas that is swollen and black throughout its length; it may be the victim of apoplexy or have succumbed to excess enthusiasm in sugar metabolism, but it will soon be swarming with bacteria. Why not drain? Their peritoneal cavity is flooded with a highly irritating fluid containing blood and trypsin; they have a chemical peritonitis, but every chemical peritonitis, whether due to the perforation of an ulcer or the experimental injection of turpentine, soon becomes bacterial. Again why not drain? In cases of this sort there is a mortality by operation of about 50%, but some patients, almost moribund, do recover; expectancy, even when gilded with infusions and transfusions, is uniformly fatal.

Recurrent Attacks of Acute Pancreatic Dysfunction with Spontaneous Recovery

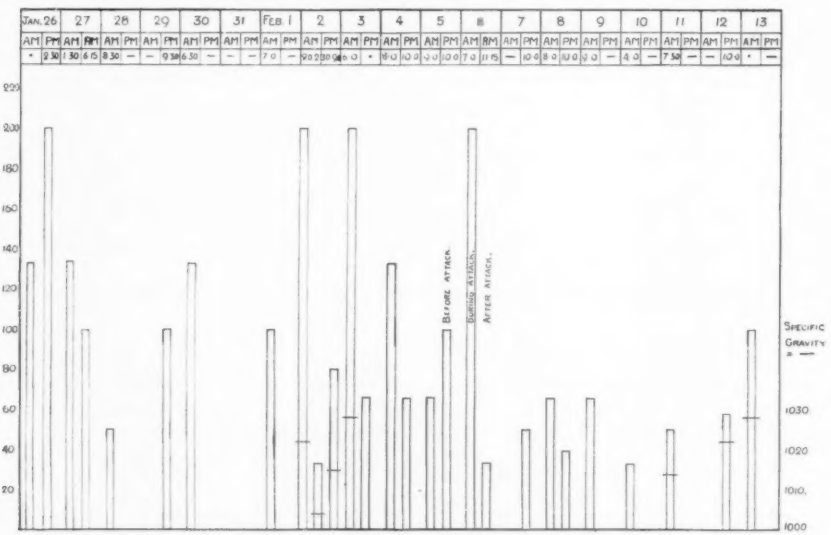
By E. R. Cullinan, M.D., and J. G. Stewart, M.B., B.S.

The case is reported for these reasons: The syndrome is seldom described; the diagnosis of a pancreatic disorder, uncomplicated by gall-bladder disease, could be made with certainty; it is an example of repeated severe pancreatic disturbance not going on to widespread necrosis; it illustrates many points in the clinical picture of acute pancreatitis.

The patient, a single woman aged 23, who had previously been well, complained in August 1928 of severe pain in the epigastrium and the *right* upper quadrant of the abdomen. There was vomiting and fever (temperature 101° F.). It is uncertain whether there was slight jaundice. X-rays showed a normal appearance of the stomach and duodenum, with stasis of the colon. In September 1928 the gall-bladder and appendix were removed by Mr. Stanford Cade. The gall-bladder was slightly distended, had a thickened wall, and contained three small stones. There were adhesions around the appendix. Mr. Cade records that the pancreas felt hard from head to tail. The patient then remained quite well until December 1928 when she had persistent

vomiting and slight fever for two weeks. She was again well until March 1929 when she had an attack of vomiting and pain in the epigastrium and the *left* upper quadrant of the abdomen. There was slight epigastric tenderness. The attack lasted three days. Following this, at intervals of about six months, she had further attacks lasting from one day to two weeks. Between the attacks she was in perfect health. Repeated X-rays showed the stomach and duodenum to be normal. In March 1934, following a severe attack, a fractional test meal showed hypochlorhydria with an excess of mucus. The W.B.C. was 3,800 per c.mm. The stools showed an excess of neutral fats. The urinary diastase was 50 units. An X-ray showed dilatation of the second part of the duodenum and also evidence of chronic constipation. In March 1936 the attacks became more frequent and more severe, and by November 1936 she was no longer completely free from pain between them. Early in 1937 she had a succession of severe attacks over a period of one month. At this time we had the opportunity to make a thorough examination of the condition. The pain nearly always started at night. The onset was sudden. The outstanding symptom was an excruciating, boring pain deep in the epigastrium radiating to the *left* upper quadrant of

URINARY DIASTASE.



the abdomen and round to the lower dorsal spine. There was nausea and occasional vomiting. During the attack there was some fever and a quickened pulse-rate. The patient was well built and not wasted. She lay still in bed. There were dark rings round the eyes. There was no cyanosis. The epigastrium looked full, but there was no rigidity. On deep palpation, there was tenderness in the epigastrium and in the left upper quadrant of the abdomen ; the right upper quadrant was free from tenderness. The abdomen was easy to examine and, on one occasion, we were quite certain that we could palpate an enlarged, tender pancreas along its whole length. There was hyperæsthesia to the left of the spine in the lower dorsal region. The pain lasted from one to seven hours and was followed for another twenty-four hours by backache in the left lower dorsal region and a feeling of general weakness. A number of chemical examinations were made and we are indebted to Dr. H. E. Archer for the estimations. The urinary diastase showed wide fluctuations, as shown in the above chart.

The high figures correspond with times of severe pain and they fall rapidly when the pain subsides. The amount of urinary diastase was not as great as is seen in cases of widespread necrosis of the

pancreas. The urine was free from sugar and bile but had an excess of indican. On January 26, during an attack, the blood lipase was raised (normal 0·2–0·3 unit) to 0·45 unit and the blood diastase (normal 3–10 units) to 15 units. The urinary diastase was 133 units. The blood-sugar was not raised; 100 mgm.%. The indirect van den Bergh reaction was at the low limit of normal; less than 0·3 unit. The vomit contained bile; also mucus and no free hydrochloric acid. During a later attack I passed a duodenal tube. There was a free flow of bile but the diastase was greatly reduced to 20 units (normal over 2,000 units). The gastric juice contained no free hydrochloric acid. Although the attacks were often preceded or followed by diarrhœa, typical pancreatic stools were not seen and several microscopic examinations showed nothing of interest. Careful X-rays, by Dr. Peter Kerley, of the pancreatic region, showed no opacities. The mucosal pattern of the stomach and duodenum was consistent with gastritis and duodenitis. There was slight dilatation of the lower end of the second part and of the third part of the duodenum, but no sign of any obstruction. The patient was known to be allergic and skin tests for sensitivity to foreign proteins showed several positive reactions. During the attacks several drugs were tried: Atropin, nitrites, and adrenaline were useless; hyoscine and heroin dulled the pain a little, morphia hardly at all; two of the newer antispasmodics, trasentin and bellergal, were helpful. Between the attacks dilute hydrochloric acid and tablets of pancreatic ferments have proved valuable. Since the beginning of 1937 the attacks have become progressively less frequent, less severe, and less prolonged. She now has only an occasional mild bout of pain and is in perfect health between times.

With regard to the ætiology we considered the possibility of a calculus, but no opacity was seen by X-rays. No swelling suggestive of a pancreatic cyst was ever felt in an abdomen easy to palpate. There was no evidence of a peptic ulcer, of a duodenal ileus, or of neoplasm. Because of the patient's temperament and because the attacks frequently followed mental fatigue, we thought of a "migrainous" basis, but dismissed the idea because of the lack of headaches, the slightness of vomiting, and the severity of the objective findings. We regarded an allergic swelling of the gland as improbable as there was no response to adrenaline. It is probable that there was an underlying chronic pancreatitis in itself insufficient to cause chronic symptoms, but with some added factor producing the acute attacks. The clinical picture exactly corresponds to that of the so-called "acute œdema of the pancreas" described first by Zoepffel in 1922, and later by Katsch 1925, Archibald 1929, and Stetten 1930. Zoepffel described four cases in which, at operation, the pancreas was seen to be swollen and œdematous. Histologically, there was inflammatory œdema of the gland without necrosis or hæmorrhage. In each of the cases the gall-bladder was inflamed. They all recovered. Stetten could find no record of this condition being a late sequel to cholecystectomy and regarded it as a forerunner of acute hæmorrhagic or necrotic pancreatitis: in the present case the symptoms have developed since cholecystectomy and are steadily improving. The cause of this "acute œdema" is obscure. It may be analogous to the experimental lesions produced by Archibald, 1929. He found that the insertion of a few drops of clean bile into the pancreatic duct of cats was followed almost immediately by a large glassy swelling of the gland. Sections showed an extensive interacinar and interlobular œdema, congestion of the vessels, and practically no necrosis. A few days later, on reopening the cats, hardly a trace of the swelling remained. If this is the mechanism in the present case, how does the bile enter the pancreatic duct? It is true that the patient had evidence of gastritis and duodenitis, but this is no explanation. Were the attacks brought on by a spasm of the sphincter of Oddi? If they were, the spasm must have been very short-lived, for we had ample evidence that there was no persistent obstruction to the normal escape of bile into the intestine. As has been said, a copious supply of bile, grossly deficient in pancreatic ferments, was obtained by a tube shortly after the beginning of an attack of pain. Two hours after the beginning, the van den Bergh reaction was at the low limit of normal. Moreover, the pain was not relieved by nitrites, drugs known to relax the sphincter.

In conclusion, we regard this as a case of the so-called " acute œdema of the pancreas "; the ætiology remains obscure.

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Mr. Harold Rodgers: My duties give me an opportunity of seeing most of the emergencies admitted to a large hospital, and it would appear to me to be possible roughly to divide the cases of acute pancreatitis into two groups—the milder cases which get well without any operation, and the more severe ones which might need an operation. In my own small experience of operating on them I have found, unlike Mr. Ogilvie, that very little drains away. My experience goes further: I have been able to follow most of my own cases to the post-mortem room and have found a great deal of débris round the pancreas a long way away from the tubes, which could not possibly have drained out of any tubes I had put in.

Section of Therapeutics and Pharmacology

President—J. W. Trevan, M.B.

[*December* 13, 1938]

DISCUSSION ON RECENT DEVELOPMENTS IN THE TREATMENT OF ADDISON'S DISEASE

Dr. S. Levy Simpson: There have been various methods of extracting the active principle of the adrenal cortex in solvents, e.g. glycerine, that would permit its action when given by mouth, but none has so far had material success. Adsorption on charcoal has proved efficacious in animals, and I have seen some degree of benefit in man from this therapy.

In 1936 Reichstein of Zürich (with collaborators) and Kendall and co-workers at the Mayo Clinic, America, obtained several crystalline fractions from crude cortical extracts, one or more proving potent when tested on adrenalectomized rats and dogs. Steiger and Reichstein (1937) finally reported that the essential constituent was a substance which they termed corticosterone, and which had a formula $C_{21}H_{28\text{-}30}O_4$, the structural formula being shown in fig. 1 A. This appeared to be identical with substance B of Kendall (1937). Although corticosterone has not yet been synthesized, a closely related compound, desoxycorticosterone, has been synthesized by Steiger and Reichstein (1937) from stigmasterol; its formula (fig. 1 B) differs from corticosterone in so far as the OH group in the nucleus is missing.

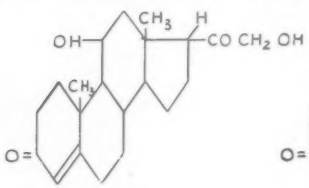

Fig. 1A.
Corticosterone.

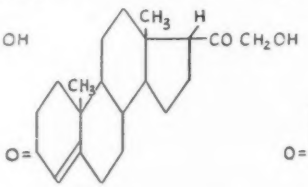

Fig. 1B.
Desoxycorticosterone.

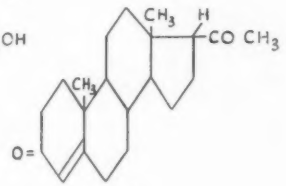

Fig. 1C.
Progesterone.

It is interesting to note that progesterone has a very similar formula (fig. 1 C), and that desoxycorticosterone acetate has a progesterone-like action in the rabbit (de Fremery and others, Miesher and others).

In adrenalectomized rats, desoxycorticosterone is far more potent than corticosterone. de Fremery and colleagues (personal communication) have found that the rat unit for corticosterone is 1,000 gamma, whereas the rat unit for desoxycorticosterone is 75 gamma. In some preliminary clinical work (Levy Simpson, 1938) I came to the conclusion that 5 mgm. of desoxycorticosterone was equivalent to more than 5 c.c. of cortical extract (cortin), and less than 20 c.c. My further work to be reported to-day, suggests that 5 mgm. of desoxycorticosterone is equivalent to 10 c.c., of cortical extract (cortin), as judged by its effect in Addison's disease. It thus appears to be less potent clinically than in adrenalectomized rat experiments where 5 mgm. is equivalent to some 70 c.c. of cortin.

The desoxycorticosterone acetate was supplied in oily solution (arachis or sesame), 5 mgm. in 1 c.c., and injected intramuscularly. In two patients the injections were painless, and in two patients local pain, redness, and induration developed. There were no adverse general reactions. Deanesley and Parkes (1937) showed that certain hormones (e.g. œstrone, testosterone) show increased and prolonged effectiveness when implanted as tablets or crystals in the subcutaneous tissue of the rat. Several clinicians (Bishop, Foss, Macbeth, Levy Simpson) have applied this work to

man with œstrone and testosterone. In the four patients, described below, I have inserted tablets of desoxycorticosterone acetate (four of 50 mgm. each per patient) in the subcutaneous tissue of the abdomen under local anæsthesia, and in the few weeks of observation this therapy appears to be as effective as daily injections. The duration of effect is uncertain, but in a castrated adult (shown at the Medical Society of London on November 28, 1938), in whom I implanted four 50 mgm. tablets of testosterone propionate, the effect appeared to be at its maximum for two months, and to gradually decline during the third and fourth months (present time).

Case 1.—This patient, Mrs. A., aged 42, was described in my original paper on desoxycorticosterone acetate as Case 1. (An additional point of interest is the existence of Addison's disease in two male cousins.) She was a case of some severity, requiring 12 grm. of salt and 20 c.c. of cortin daily. The last dose of cortin and of salt was given at 9 a.m. on May 11. From May 13 to 21 the patient was given 3 mgm. of desoxycorticosterone daily. There was a gradual deterioration in her condition, weakness, irritability, nausea, and a sensitivity to cold developing. The pulse became rapid, and somewhat irregular, and the systolic blood-pressure had fallen from 120 to 110. On the afternoon of May 21 she was given 12 mgm. of desoxycorticosterone acetate, and this was followed in ten minutes by a partial collapse with feeble pulse, but there was then progressive improvement. From May 22 to 25 she received 6 mgm. corticosterone acetate twice daily, and her general condition was reasonably good, but she was not as well as on cortin and salt; she was under the definite impression that desoxycorticosterone acted much more rapidly than cortin, but its action did not last as long, the maximum effect wearing off in a few hours. On the 25th and 26th she had 6 mgm. corticosterone acetate daily, and her salt mixture. Her condition improved slightly. On May 27 she returned to cortin, 20 c.c. daily, together with the salt mixture. There was an almost immediate improvement in her condition, and after a few days she was feeling as well as ever. The blood-pressure throughout had remained between 115 and 120 mm. of mercury, except for a transitory fall to 110 on May 21.

The blood chemistry, in spite of the patient's poor clinical condition at one period, showed no adverse change. Thus, on May 13, the serum sodium was 307, the serum chloride 365, and the blood-urea 18 mgm./100 c.c.; on May 16 the figures were 307, 352, and 28 respectively, and on May 21, 322, 368, and 22. On October 12 of this year she again came under my observation, and 5 mgm. of desoxycorticosterone acetate given twice daily then appeared to be an adequate substitute for 20 c.c. of cortin, salt, however, being continued. The blood chemistry remained normal. After some days of treatment, however, the sites of injection became painful and lumpy. On November 9 I inserted four tablets of 50 mgm. of desoxycorticosterone acetate subcutaneously. Injections were stopped, but salt was continued. The patient remained in good condition, and on November 29 the serum sodium was 312, chloride 364, urea 26 mgm.%. She then underwent a plastic perineal operation, receiving an extra 40 c.c. of cortin on the day of operation. Apart from a dose of cortin (20 c.c.) during a sore throat and catarrhal attack, and another just before a menstrual period, she has been kept on salt only and has remained moderately well. The extra cortin produced appreciable improvement. Since the rate of disintegration of the tablets does not depend upon physiological needs, it is reasonable to give extra cortin or desoxycorticosterone during infections or periods of strain.

Case 2.—This patient, J. M., was a male aged 25. He was described as Case 2 in my original paper on the use of desoxycorticosterone acetate in Addison's disease.

In 1934 he was diagnosed as Addison's disease, and responded to 12 grm. of salt and 5 c.c. of cortin daily, maintaining fair but not robust health. On June 22, 1938, the 5 c.c. of cortin was replaced by 6 mgm. of desoxycorticosterone acetate daily. There was an almost immediate gain in strength and well-being and his weight increased by 14 lb. in 14 days; the blood-pressure rose from 100/60 to 115/70, and the pigmentation decreased. The serum sodium rose from 296 to 309 mgm.%. On returning to 5 c.c. cortin there was a decrease in weight and well-being, but he felt that there had been some permanent benefit from the desoxycorticosterone. On November 24, while on salt and 5 c.c. cortin daily, the serum sodium was 295 mgm.%, the serum chloride 345 mgm.%, and the urea 41 mgm.%. On that day I inserted four tablets of 50 mgm. of desoxycorticosterone acetate in the subcutaneous tissues. The patient continued with salt. On December 7 the patient was seen again; he was in good condition and had put on 5 lb. in weight; the serum sodium had risen to 324 mgm., the chloride to 382 mgm.%, and the blood-urea had fallen to 30 mgm.%, a very significant improvement in the blood chemistry.

Case 3.—C. T. M., male, aged 54. An account of this case was presented by me to this Section in July 1936 (Vol. 29, 1142, 46, Case IV). Briefly he is a very severe example of Addison's disease, maintained for periods on salt only and at others with 10 c.c. of cortin daily in addition. On September 8, 1938, by the courtesy of Dr. J. G. Leebody, he was admitted to Willesden General Hospital, complaining of weakness, loss of weight, anorexia, and nausea ; there was also a chronic cough, due to non-tuberculous bronchitis. For some months he had been on 10 grm. of salt daily, which was continued, but no cortin. In the first week his weight fell 2 lb. to 7 st. On September 16 daily injections of 5 mgm. of desoxycorticosterone acetate were commenced, and continued until the 29th, when the patient had to return home for domestic reasons. His weight on leaving was 7 st. 6 lb. The blood-pressure was 140/80 on admission and remained unchanged. The patient felt stronger and helped in the ward. His appetite was better and pigmentation less intense. He returned to hospital on October 10, feeling less well but better than on his first admission. The only treatment in this interval had been salt. His weight had fallen to 7 st. 1 lb. On October 12 the daily injections of 10 mgm. desoxycorticosterone began. On October 21 the weight had increased to 7 st. 6 lb., and the patient felt much better. From October 22 to October 29 there was substituted 10 c.c. of cortin daily ; the patient was not so well, and the weight fell to 7 st. 4 lb. ; from October 30 to November 8, 20 c.c. of cortin were injected daily. The weight rose to 7 st. 6 lb. and the patient felt better than for some time. On November 8, I implanted four 50-mgm. tablets desoxycorticosterone in the subcutaneous tissue. The weight rose to 7 st. 8 lb. by November 15, but on stopping the salt it fell in three days to 7 st. 1 lb. He, however, continued to feel very well, and was discharged on November 18. He was seen by me again on November 30, not having had any salt or other treatment in the meantime. He felt extremely energetic and better than ever he could remember. His weight was 7 st. 5 lb., and the blood pressure had apparently risen to 160/90. The following data suggest that the inserted tablets alone were not sufficient therapy to maintain the level of serum sodium and chloride, but also illustrate that the blood chemistry is not necessarily a good indication of the clinical condition.

MINERAL METABOLISM (CASE 3).

Date	Na	Cl	K	Urea	Treatment
September 10	308	335	–	–	Salt only. Poor clinical condition
September 16–29	–	–	–	–	Salt + 5 mgm.desoxy.
October 10	314	362	–	31	Salt only
October 22	293	338	–	31	Salt + 10 mgm. desoxy.
November 4	315	355	–	38	Salt + 20 c.c. cortin
November 7	Insertion of desoxycorticosterone tablets subcutaneously				
November 8	321	357	–	35	Salt + 20 c.c. cortin
November 23	284	337	–	44	Nil
December 1	296	348	–	30	Nil. Good clinical condition

Case 4.—The patient, M. B., girl aged 18, complained of lassitude for six months ; loss of weight from 11 st. 3 lb. to 8 st. 12 lb. The appetite was capricious, and she had been worried by some increase in pigmentation. Menstruation was normal. There was no familial history of significance. Dr. K. Jones, of Nottingham, diagnosed Addison's disease, and by his courtesy the patient came under my care at the Willesden General Hospital. The pigmentation was seen to be present on the inner lip and cheek and the blood-pressure was 80/55 on admission, September 22, 1938. Radiogram (Dr. Rohan Williams) showed calcification of the left suprarenal gland. The salt, which had produced slight improvement previously, was stopped, and no treatment was given for the first week. The patient lost 2 lb. in weight, felt weaker and somewhat drowsy ; she also complained of nausea with occasional vomiting. On September 28 the serum sodium was 284 mgm.%, serum chloride 320 mgm.%, and the blood-urea 30 mgm.%. 5 mgm. of desoxycorticosterone acetate was injected daily on September 28 and 29. The condition, however, deteriorated. From September 30 to October 2, 5 mgm. of desoxycorticosterone acetate was given twice daily. There was some improvement in the condition, but the weight persisted at 8 st. 8 lb. From October 3 to 11, 10 mgm. of desoxycorticosterone was injected twice daily. The patient immediately felt better and stronger. Nausea disappeared and the weight increased to 8 st. 11 lb. On October 11 the serum sodium was 301 mgm.%, the serum chloride 357 mgm.%, and the blood urea 22 mgm.%. The sites of injection, however, were lumpy, red, hot, and painful, and after reducing the dose to 5 mgm. twice daily, it was discontinued on October 13, the general condition having deteriorated. During the next twelve days the patient received 10 c.c. of cortin daily. She appeared to be in better condition on cortin than on desoxycorticosterone as far as superficial appearance and sense of well-being were concerned, but the weight decreased to 8 st. 8½ lb. On

October 24 the serum sodium was 300 mgm.%, the serum chloride 351 mgm.%, and the blood-urea 20 mgm.%. On October 28 I inserted four 50-mgm. tablets of desoxycorticosterone in the subcutaneous tissues. 10 c.c. of cortin were given on October 25 and 26 but not subsequently. The weight fell 2 lb. during the next few days, but the patient felt well and strong and there were no symptoms. She left hospital on November 3.

In spite of the apparent clinical improvement, the serum sodium was then 286 mgm.%, chloride was 356 mgm.%, and urea 22 mgm.%. The blood-pressure during the stay in hospital had not changed appreciably, varying from 80/60 to 90/65. No treatment (neither cortin nor salt) was given at home, and on November 29 the patient wrote that her weight had increased by 5 lb. and that she was feeling very well. Dr. Jones wrote on December 4 that the patient presented no symptoms, her pigmentation was less, and the blood-pressure 106/76. On December 11 Dr. Jones reported that the patient continues well, weight 8 st. 11½ lb., blood-pressure 110/78.

Conclusions.—Desoxycorticosterone acetate is potent in Addison's disease; 5 mgm. appear to be equivalent to 10 c.c. of cortical extract (cortin). Its anabolic action, well marked in Case 2, reminds one of the anabolic action of testosterone propionate (Levy Simpson, 1938). From clinical impressions (especially Cases 1 and 4), I do not believe that desoxycorticosterone acetate is the only essential constituent of potent cortical extracts. The insertion of tablets of desoxycorticosterone acetate subcutaneously appears to be as effective as daily injections. The duration of effect is yet undetermined, but from analogy with testosterone a period of two months' effectivity with a gradual decline from then onwards might be anticipated. Since the rate of disintegration and absorption of the tablets depends on physical laws and not on the physiological needs of the patient, extra strain should be met by supplementary injections when necessary. Salt appears to be of value in enhancing the effect, or reducing the dose, of desoxycorticosterone acetate.

Further advances or modifications of therapy might be anticipated in some directions: (1) Modification of the molecule of desoxycorticosterone to render it potent by mouth, cf. testosterone and progesterone; (2) preparation of other esters of desoxycorticosterone with more prolonged action; (3) inunction of suitable preparations of desoxycorticosterone or its esters; (4) the synthesis of similar compounds of greater potency.

I have much pleasure in acknowledging the generosity of Messrs. Ciba and Organon in supplying ampoules of desoxycorticosterone acetate, and the latter firm also for tablets of this substance. Dr. E. N. Allott has made the scientific control of these experiments possible by his much-valued co-operation on the biochemical side, he being responsible for all estimations of sodium and chlorine, and I am indebted to him. The work was carried out under the auspices of the Therapeutic Trials Committee of the Medical Research Council.

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Subsequent to the discussion, Dr. Levy Simpson said it was just as well that the different advances in therapy had come step by step, because it had permitted us to learn a good deal about the potentialities of the various therapeutic weapons. There was a tendency, however, to forget some of the lessons learned in the past eight years. Thus the tendency of the Addison patient to become allergic in crisis was well recognized, and intravenous therapy at that phase was in his view contra-indicated, unless the patient was *in extremis*. In the latter circumstances, a fatal

and anaphylactic reaction must be risked, because some patients recover in spite of this. He had previously pointed out that his own technique in crisis was to give 10 or 20 c.c. of cortin intramuscularly every four hours and no intravenous therapy. Most cases under this treatment recovered. Purgatives were always strongly contra-indicated, as had been long realized, the danger of precipitating a crisis being a real one. Even minor operations, prior to cortin, were frequently fatal, but that was no longer true. Some years ago he had recorded that a patient had undergone hysterectomy, being treated by cortin only, without salt, the anæsthetic being gas and oxygen and ether, and had made a complete recovery. This was true also of Case 1, under the circumstances described. These facts also apply to the use of morphia. It has also been well recognized at a previous discussion at this Section on salt therapy (1936, **29**, 45), that the serum sodium and chloride concentrations were not necessarily an indication of the clinical condition. In this connexion it was well to remember that, unlike the rat and the dog, an adrenalectomized marmot died with a normal serum sodium and chloride, but a very low blood-sugar.

As regards the efficacy of this new synthetic hormone, drawing one's evidence from all the cases presented by the various speakers, one was forced to the conclusion that it was not the only essential constituent in a potent cortical extract.

Addendum 27.3.39: The beneficial effect of insertion of 200 mgm. of desoxycorticosterone acetate subcutaneously lasted for some two and a half to three months. In severe cases this appears to maintain only moderate health; salt and even supplementary injections of desoxycorticosterone may be necessary. The rate of absorption is probably constant, and extra effort or infection calls for supplementary therapy.

Inunction of desoxycorticosterone acetate was tried by me and found to be efficacious. The dose is some four times (or more) the dose by injection. It was prepared by Messrs. Ciba in ampoules of 1 c.c., containing 20 mgm. of desoxycorticosterone acetate dissolved in 100 mgm. of benzyl alcohol. The inunction, performed by the patient, takes some ten to twenty minutes, and there may appear to be a lessening of pigmentation at the site of inunction. Neither by the method of inunction, nor by that of subcutaneous insertion, was there evidence of a refractory phase, as is sometimes observed after two weeks' injections. It is suggested that this apparent refractory phase is associated with the local reactions at the sites of injections that some patients display. Nevertheless the additional experience of treatment by subcutaneous implantation or inunction of desoxycorticosterone acetate still leaves the question open as to whether this is the only maintenance hormone of the adrenal cortex.

Dr. John F. Wilkinson: Since 1933 I have thoroughly investigated some 30 patients with Addison's disease seen in my clinic or in the wards of the Manchester Royal Infirmary. These cases fall into two main groups; (1) those not given cortical hormone and (2) those given the natural or the synthetic suprarenal cortical hormone.

Before the cortical hormone became available, treatment of Addison's disease was very unsatisfactory. In my first group of patients the mortality was 100%. This group consists of 13 patients who were not treated with cortical hormone in any form. All but one died within eight weeks of admission to hospital. Of these patients four had simple suprarenal atrophy, three had acute pulmonary tuberculosis, two malignant metastases in both glands, and there was one patient each with acute miliary tuberculosis of all the viscera and peritoneum, advanced subacute combined degeneration of the spinal cord, and pancreatitis with gastric ulcers respectively. This group contains, however, a number of obviously hopeless cases who would not have responded even if active cortical extracts had been available.

The preparation of active extracts of suprarenal cortex (1930) for the treatment of Addison's disease by Swingle and Pfiffner completely changed the possibilities of treatment. The cost of these extracts, however, is a very important item since many patients probably receive insufficient doses, with consequently poorer results.

The extracts may be given intravenously (with slightly quicker results and enabling larger doses to be given at once) or intramuscularly with a slightly more prolonged action. Both routes are quite satisfactory. I have tried cortin adsorbed on charcoal and given orally, but without any effect.

My second group of cases consists of 13 patients, all of whom showed the typical features of Addison's disease—asthenia, muscular weakness, gastro-intestinal disturbances, severe pigmentation, loss of weight, low blood-pressure, subnormal temperature, and a variable degree of abnormality in the blood chemistry. All were treated with active cortical extracts such as cortin (Organon).

Some of these patients were used in an investigation on behalf of the Medical Research Council, and the results of using cortical extracts were reported last year (*Lancet*, 1937 (ii), 60). Further new cases are added here. This group may be subdivided into two, a group of nine patients who have been treated with suprarenal cortical extracts and are alive and well after periods of twelve months to four years and eight months, and a group of four patients who despite cortical hormone therapy ultimately died. These four died after four, four, thirty-two, and eight weeks, having received a total of 450, 465, 3,015, and 480 c.c., respectively of cortical extract. Two then died from acute crises with hyperpyrexia after adequate therapy ; their suprarenal glands were completely caseous and very large amounts of cortin failed to have effect. One case had responded well to cortin though (having had over 3 litres of cortin) without salt, but died suddenly from cardiac failure following acute auricular fibrillation. The fourth case may not have had sufficient cortin replacement therapy of his atrophied suprarenal glands.

Table I summarizes the treatment of the nine surviving cases. Four of these have not had or required any cortin for forty-eight, twenty-eight, thirty-six, and twelve months respectively, a fact which raises an interesting possibility as to the return of some cortical function in these patients.

TABLE I.—ADDISON'S DISEASE. PATIENTS SURVIVING ON DECEMBER 1, 1938, AFTER TREATMENT WITH CORTIN.

Case	Sex	Age	Total cortin (c.c.)	Survival since treatment (months)	Present treatment		Present condition
					Salt (grm.)	Cortin (c.c.)	
18	F.	26	940	56	15	Nil (48 mths.)	V. well
19	F.	40	140	50	15	Nil (28 mths.)	V. well
20	M.	35	65	46	7·5	Nil (36 mths.)	V. well
21	F.	33	748	29	15	4 weekly	V. well
22	F.	48	605	31	7·5	Nil (12 mths.)	V. well
23	M.	35	6060	14*	15	20 daily	*See* text
24	F.	46	2487	18	7·5	10 alt. days	V. well
25	F.	25	935	12	7·5	10 alt. days	Well
26	M.	52	1500	14	7·5	10 alt. days	Well

* To September 1938.

Case Summaries

Case 18 (A.D. 11 ; *Lancet*, 1937 (ii), 61).—A housewife aged 26 ; first seen on May 16, 1934 ; pulse 130 ; blood-pressure 80/60 ; weight 7 st. 13 lb. Blood-urea 96 ; chlorides 440 ; sugar 83 ; serum sodium 305 ; phosphates 5·5 ; potassium 27 mgm./100 c.c. Urinary chloride excretion 2–3 grm. daily. She had a practically normal blood-count, achlorhydria gastrica, normal basal metabolic rate, no definite evidence of tuberculosis or calcification in lungs, or suprarenal glands, increased glucose tolerance.

Treatment.—On intensive treatment with cortin (initially 40–50 c.c. daily) her blood chemistry became normal. Salt (5–15 grm.) daily was added to her diet later, and the cortin gradually reduced. The last dose of cortin was given on November 27, 1934, and since then she has taken 15 grm. salt daily in addition to plenty of fruit and a normal diet. Her colour is very much lighter, although she is still rather darker than the normal individuals, she is free from symptoms, and does all her own housework without fatigue. Her latest blood-pressure is 120/80 and weight 8 st. 8 lb.

Case 19 (A.D. 12 ; *Lancet*, 1937 (ii), 61).—Housewife, aged 40 ; pulse 64, blood-pressure 95/65,

weight 7 st. 3 lb., temperature 98° F. She had slight anæmia, hypochlorhydria gastrica, normal glucose tolerance test, basal metabolic rate and urine. Urinary chloride excretion 1·2–4·0 grm. daily. Blood-urea 34, sugar 80, phosphates 3·8, sodium 324, chlorides 480, potassium 21 mgm./100 c.c. X-rays showed fine mottling in the lungs suggestive of tuberculosis, but no evidence of calcification in the suprarenal areas.

Treatment.—She was given 15 grm. salt daily for four weeks without any improvement, when eucortone (10 c.c. daily) was commenced and produced rapid clinical improvement. Discharged on 15 grm. salt daily, which she did not take regularly; she relapsed in June 1935. (Blood-pressure, 94/60; weight 7 st.) She was once again given 15 grm. of salt daily and also 5 c.c. cortin intramuscularly monthly with rapid remission. On June 13, 1937, she was very well, blood-pressure 110/80, weight 7 st. 8 lb., normal blood chemistry. Eighteen months later (1938) she was still maintaining her improvement (blood-pressure 100/70; pigmentation almost gone), but has not had any cortical extracts since July 1936.

Case 20 (A.D. 18; *Lancet*, 1937 (ii), 61).—Male presser, aged 36, was a more chronic type of case with typical features of the disease; weight 8 st. 3 lb.; blood-pressure 100/65; pulse 76; temperature 97° F., urine normal, urinary chloride excretion 2–4 grm. daily; basal metabolic rate and glucose tolerance test normal; hypochlorhydria gastrica. There was a moderate degree of megalocytic anæmia. Blood-urea 38, sugar 100, phosphates 4·1, sodium 332, chlorides 454 mgm./100 c.c. X-rays of chest and loins were normal.

Treatment.—Eucortone 5 c.c. intramuscularly and 7·5 grm. salt daily. He improved considerably and has not had any cortical extracts since 1935. He has maintained his improvement. His last blood-pressure was 106/70; blood chemistry normal.

Case 21 (A.D. 23; *Lancet*, 1936 (ii), 967; 1937 (ii), 61).—Housewife, aged 32, first diagnosed on January 14, 1936. Radiograms of chest were normal; there was irregular calcification at the upper pole of the left kidney along the outer border; there was slight evidence of calcification above the upper pole of the right kidney. Pulse 72; blood-pressure 125/75 (few days later 95/?), weight 7 st. 12 lb., temperature 97·6° F. Urine normal. Urinary chloride excretion 0·9–5 grm. daily. Normal blood-count, basal metabolic rate, and glucose tolerance test; hypochlorhydria gastrica. Blood-urea 24, sugar 77, chlorides 460, sodium 330; phosphates 3·8 mgm./100 c.c.

Treatment.—She was given 20 c.c. cortin daily initially, but this was rapidly reduced. She was discharged April 9, 1936, on 15 grm. salt daily, fruit juices (vitamin C) and 2·5–5 c.c. cortin fortnightly. In August 1936 the cortin was discontinued. In February 1937 she developed a severe cold with temporary fall of blood-pressure and was given 2·5–5 c.c. Cortin weekly again. Since then she maintained perfect health, and the pigmentation diminished very considerably (completely from mucous membranes) until February 2, 1938, when she had a blood-pressure of 140/80, weight 9 st. 0 lb., and was feeling very well. However, on February 20, 1938, she developed another severe cold, nausea, vomiting, enlarged cervical glands, and blood-pressure 90/70. Readmitted to hospital immediately, she was given 10 c.c. cortin daily, the salt being temporarily discontinued owing to the vomiting. She rapidly improved and was discharged March 10, 1938, on 15 grm. salt and 5 c.c. cortin twice weekly, which since then has been gradually reduced to 4 c.c. monthly. She is very well at the present time with a blood-pressure of 125/85 and weight 9 st.

Case 22 (A.D. 24; *Lancet*, 1936 (ii), 967; 1937 (ii), 61).—Housewife, aged 48, admitted November 14, 1935; weight 7 st. 12½ lb.; pulse 92; blood-pressure 120/70 (105/65 after admission). Temperature 97° F.; urine normal; urinary chloride excretion was 1·75–2·7 grm. daily. Blood-count and basal metabolic rate normal; achlorhydria gastrica; increased glucose tolerance; blood-urea 20, sugar 81, phosphates 4, sodium 328, chlorides 460 mgm./100 c.c. Radiograms of chest and loins normal.

Treatment.—She was given 10 c.c. and then 20 c.c. cortin daily. She gradually improved and the cortin was slowly reduced to 5 c.c. on alternate days when salt (15 grm. daily) was added to her diet. She was discharged February 12, 1936, very much improved, weight 8 st. 3½ lb. blood-pressure 135/75. The cortin was discontinued on August 25, 1936, but she continued to take 7·5 grm. salt daily. In January 1937 her weight was 8 st. 8 lb. and blood-pressure 145/85; she has maintained this condition to date.

Case 23.—An engineer, aged 35, was admitted in July 1937. He had been well until April 1937, when he began to feel abnormally sleepy, was very easily tired, and finally collapsed at work. In May he noticed that the skin was going darker in colour and he was getting some blurring of

vision. His appetite became poor, and he lost weight, while nausea and vomiting became frequent. The pigmentation and drowsiness increased rapidly, and on admission he was semi-comatose, only answering questions after great effort.

He was emaciated and deeply pigmented. The pigmentation was generalized and very dark brown, almost black over knuckles, knees, axillary folds, face, and at pressure points; the buccal mucosa was deeply pigmented.

Hair was dark brown; eyes brown; teeth good, tongue dirty. Breath smelt of acetone. Pulse 84, blood-pressure 64/34; temperature 97° F.; weight 7 st. 13 lb. The heart sounds were very faint, and the lungs were normal. The abdomen moved freely, the spleen and liver were not enlarged. Nervous system: Reflexes rather depressed.

Urine: Specific gravity 1020; acid reaction, no abnormalities.

Blood-count: R.B.C. 5,776,000; Hb. 105%; W.B.C. 14,400; polys. 38·5; lymphos. 44·5; large monos. 15·5; eosinos. 1·5. Aniso- and poikilocytosis slight; nucleated red cells nil; platelets abundant.

He had a negative Wassermann reaction, achlorhydria gastrica, and a basal metabolic rate of plus 18%.

Bacteriological examination of fæces, throat swabs, &c., were negative. Blood-urea 98; sugar 81; non-protein nitrogen 66; chlorides 368; serum sodium 264; plasma phosphates 5 mgm./100 c.c. (*see* Table II).

On 29.7.38 the blood-urea had risen to 178 mgm./100 c.c. and non-protein nitrogen to 110 mgm.

No radiological evidence of pulmonary tuberculosis or calcification in suprarenal area. There was a calcified gland in the right sacro-iliac region.

TABLE II.—CASE 23 (*Abridged*)

Date	Blood-pressure	Treatment cortin (c.c.)	Weight	Urea	Chloride	Sodium	Potassium
26.7.37	64/34	30		98	368	264	
27.7.37	65/35	30					
28.7.37	82/45	30					
29.7.37	66/35	60 daily		178	376	268	28
3.8.37	60/32	60 daily	7 st. 13 lb.	154	378	270	28
9.8.37	70/32	60 daily		110			
18.8.37	82/50	20 daily		34			
26.8.37	95/45	10 daily		27			
27.8.37	95/70	10 daily					
28.8.37	112/80	5 daily					
4.9.37	103/50	2·5 daily	7 st. 11 lb.	36	458	320	21
11.9.37	95/50		7 st. 11 lb.	32	478	328	20
16.9.37	90/58	2·5 alt. days	7 st. 12 lb.				
27.9.37	105/60		7 st. 12 lb.				
28.12.37	68/30	26		120	420	390	26
29.12.37	70/35	50					
30.12.37	65/30	70					
31.12.37	66/30	60 daily		144			
3.1.38	68/38	60 daily		120			
6.1.38	60/35	60 daily		50			
10.1.38	70/35	30		39			
11.1.38	75/35	30		25			
12.1.38	80/40	30					
13.1.38	75/38	30		28			
14.1.38	78/40	20 daily					
18.1.38	90/45	10	7 st. 1 lb.				
19.1.38	95/55	10					
20.1.38	95/55	5 daily					
22.1.38	—	5 alt. days		22	487	330	20
15.3.38	98/70	10 daily		38			
29.3.38	60/?	30 daily					
22.4.38	115/65	10–15 daily		30			
23.6.38	75/50	30 daily		36	480	330	20
28.7.38	110/70	20 daily		26			
30.8.38	125/90	20 daily	8 st. 10 lb.	30			

Treatment.—The patient was desperately ill and almost completely comatose in the first forty-eight hours. He was given 60 c.c. of cortin daily in divided doses (*see* Table II) and responded

slowly although for the first week or two he was liable to attacks of nausea and slight vomiting, especially if the cortin was delayed or reduced. Simultaneously with his clinical improvement the blood chemistry returned to normal, the blood-urea being 34 mgm. at the end of twenty-four days, when the cortin was reduced from 60 c.c. to 20 c.c. daily. As he improved clinically and chemically, the cortin was gradually reduced until his discharge (6.10.37), when he was taking 2½ c.c. daily. His weight was 10 st. He was instructed to take 10–15 grm. salt daily. The pigmentation was much less marked and the patient was brighter and stronger. He was given 5 c.c. cortin each week, the blood-pressure remaining about 115/80, weight about 10 st., and he felt very well.

On December 3, 1937, he complained of a severe chill with general malaise and loss of weight. The pigmentation was slightly more marked and blood-pressure 95/60. He was immediately readmitted. The clinical and laboratory findings were similar to the original ones, the blood-urea being 46 mgm. He improved very much on increased doses of cortin, and was discharged ten days later. On December 28, 1937, he was again readmitted with marked loss of energy, increased loss of weight, increased pigmentation, loss of appetite, nausea and vomiting following a further chill. His blood-pressure was 70/35, pulse 92, and blood-urea 144 mgm. The other blood changes were similar.

He was given 40 c.c. cortin intravenously and 20–30 c.c. intramuscularly daily for thirteen days, when the blood-urea was 30 mgm., the dose being reduced first to 30 c.c. daily intravenously for five days, and then to 20 c.c. intravenously daily. He was ultimately discharged (28.1.38) on a full salt diet and 5 c.c. cortin daily. This was insufficient to maintain his condition and he lost weight slowly. Occasional vomiting occurred, the pigmentation tended to increase, the systolic blood-pressure remained about 85/105, and the blood-urea began to rise to 38 mgm. The cortin was increased to 10 c.c. daily and later 30 c.c. daily in March 1938. On this dosage his blood-pressure increased to 115/65, weight increased, pigmentation diminished, and he felt much better. Many attempts were made (between March and October 1938) to reduce the dose, but it was never possible to get it below 20 c.c. intramuscularly daily without relapses occurring. In August 1938 he was very well, weight 8 st. 10 lb., blood-pressure 125/90, blood-urea 30 mgm. (*see* later, under desoxycorticosterone).

Case 24.—A housewife, aged 46, complained of increasing and variable lethargy, nausea and anorexia for twelve months. Six months before admission she noticed that the skin was becoming browner and four months later it had increased considerably, together with the onset of palpitation, dyspnœa, severe asthenia and muscular weakness, loss of weight, nausea, slight vomiting. She was very constipated ; the menopause occurred at 37 years of age.

On examination.—Deeply pigmented—very lethargic and only answered questions with considerable effort. She had lost weight, and was 6 st. 12 lb. ; pulse 86, regular ; blood-pressure 85/? ; temperature 97·6° F. No enlarged glands or tonsils, tongue clear, jaws edentulous. The dark brown pigmentation was generalized, but was especially marked on the dorsum of the hands, elbows, shoulders, over the dorsal vertebral spines, axillæ, knees, dorsum of toes, face and neck. The buccal and vaginal mucous membranes contained patches of pigment. No definite abnormalities were noted in the heart, lungs, abdomen, or nervous system, apart from a palpable right kidney and indefinite plantar responses.

Urine : Specific gravity 1020 ; acid reaction ; no abnormalities. Urinary chloride excretion was 1·26–3·7 grm. daily. Blood-urea 40 ; sugar 77 ; sodium 322 ; chlorides 452 ; potassium 22 ; phosphates 3·9 mgm./100 c.c. She had a negative Wassermann reaction, achlorhydria gastrica, and a basal metabolic rate of plus 11%. Radiograms of the chest and loins showed slight infiltration at the right apex suggestive of early pulmonary tuberculosis ; there was no evidence of suprarenal calcification.

Blood-count : R.B.C. 4,512,000 ; Hb. 84% ; W.B.C. 8,800 ; polys. 46·5 ; lymphos. 42 ; large monos. 7·5 ; eosinos. 3·5 ; basos. 0·5%. Platelets abundant.

Treatment.—She was given 10 c.c. cortin daily intravenously, later intramuscularly, for fifteen days and showed marked improvement, particularly losing her lethargy and weakness, and putting on weight. The dose of cortin was gradually reduced to 5 c.c. daily, and ultimately to 2½ c.c. twice weekly with 7·5 grm. salt daily. The blood-pressure was then 110/80. From September 27, 1937, she received 2½–5 c.c. cortin intramuscularly weekly, and she gradually gained weight although the blood-pressure remained about 100/75. In February 1938, after a severe attack of influenza, she relapsed and was readmitted (March 1, 1938). Her weight had fallen to 6 st. 12 lb. ; blood-pressure 84/62, temperature 96·6° F., and pulse 92. Her blood-urea

was 60 mgm., phosphates 6·0 ; chloride 442 ; serum sodium 320 mgm./100 c.c. She was given 10 c.c. cortin intramuscularly and 7·5 grm. salt daily for three weeks, again with improvement in the clinical condition, weight and blood-pressure, and a fall in the blood-urea. The cortin was reduced to 5 c.c. on alternate days, but on account of slight nausea, vomiting, and a tendency for the blood-pressure to fall readily, the cortin was increased to 20 c.c. daily on April 28, 1938, when the systolic blood-pressure was about 60 and the patient still persisted with a slight cold. Her blood-pressure then rose rapidly to 120/80 (May 12, 1938), and weight 7 st. 10 lb. She was discharged on a dose of 20 c.c. cortin weekly. The systolic blood-pressure remained about 100/70 on this dose and she felt quite well, but as the weight fell a little, she was put on to 10 c.c. cortin on alternate days with 7·5 grm. salt daily, and remains very well to date (December 1938), Table III.

TABLE III.—CASE 24.

Date	Blood-pressure	Treatment cortin (c.c.)	Weight	Urea	Chloride	Sodium	Potassium	Phosphates
8.7.37	85/?	10 daily	6 st. 10 lb.	40	452	322	22	3·9
9.7.37	75/65							
23.7.37	105/75	5 daily*	7 st. 11 lb.					
29.7.37	107/75	5 alt. days	7 st. 3 lb.					
6.8.37	110/80		7 st. 3 lb.	30	472	326	19	— Sug. 86 m.
10.8.37	80/65	2·5 alt. days						
21.8.37	105/80	2½ every 4th day	7 st. 2 lb.					
10.9.37	110/85	2·5 weekly	7 st. 6 lb.					
29.10.37	98/68	5 weekly	7 st. 7 lb.					
4.12.37	110/80	5 weekly	7 st. 8 lb.					
4.2.38	110/80	2·5 weekly	7 st. 6 lb.					
1.3.38	84/62	10 daily	6 st. 12 lb.	60	442	320	—	5·0
5.3.38	84/64	10 daily	6 st. 12 lb.	46				
19.3.38	84/60	5 daily	7 st.	36				
31.3.38	90/60	10 alt. days	7 st. 3 lb.					
14.4.38	60/?	10 daily	7 st. 5 lb.					
28.4.38	60/?	20 daily	7 st. 7 lb.					
12.5.38	120/80	15 daily	7 st. 10 lb.					
26.5.38	98/74	20 weekly						
29.6.38	95/65	10 alt. days	7 st. 7 lb.					
16.11.38	95/65	10 alt. days	7 st. 10 lb.					

* 7·5 grm. salt given daily from July 19, 1937.

Case 25.—A female, aged 25, was seen December 12, 1937, on account of increasing pigmentation, lassitude, nausea, and vomiting.

She had been under treatment since 1930 for tuberculous disease of the spine and right knee-joint and had worn a spinal brace ever since ; in 1932 she had cystitis, and in 1935 she was treated for tuberculosis of the left knee. There was no evidence of active disease of bone when referred to me.

Since 1935 the skin had been becoming more deeply pigmented, and in the autumn of 1936 she began to have frequent headaches, nausea, vomiting, loss of appetite, constipation, and dyspnœa on exertion. Asthenia and muscular weakness developed three months prior to admission, with only slight loss of weight.

On examination.—A small woman with old spinal caries, the xiphoid angle was small, the lower ribs almost touching the iliac crests ; right knee-joint ankylosed. The lower dorsal spine was rigid. Her skin was pigmented dark brown all over, but especially affecting elbows, knuckles, knees, shoulders and back where brace presses, and face, but pigmentation was not very excessive in the areolæ. The mucous membranes of the mouth and vagina showed dark patchy pigmentation. This pigmentation was particularly marked, especially opposite the teeth and along the lips. The conjunctivæ were also pigmented. Teeth were carious, tonsils not enlarged ; tongue clean, moist but pigmented at the sides ; pulse 65, regular, good volume ; blood-pressure 95/60 ; temperature 98° F. ; weight 5 st. 12 lb. The lungs were clear, the abdomen and the central nervous system were normal. The heart did not show any gross abnormality.

Urine : Specific gravity 1015 ; alkaline reaction ; albumin + ; pus + ; sugar nil ; acetone +. A catheter specimen showed Gram-negative bacilli in films, and culture yielded *B. coli*. Urinary chloride excretion was 1·25–2·05 grm. daily. Blood-urea 82 ; sugar 70 ; sodium 328 ; chlorides 426 ; potassium 24 ; phosphates 3·7 mgm./100 c.c.

Blood-count: R.B.C. 4,300,000; Hb. 78%; W.B.C. 8,200; polys. 53·5; lymphos. 86·5; large monos. 5·0; eosinos. 4·5; basos. 0·5%. Aniso- and poikilocytosis fairly slight; no nucleated red cells; platelets abundant. Her basal metabolic rate was increased by 22%, and she had a negative Wassermann reaction, achlorhydria gastrica, and normal electrocardiogram. Radiograms of the chest and loins showed the 9th and 10th dorsal vertebræ diminished in size and increased in density; the suprarenal area showed no abnormal shadows. Glucose tolerance test: Fasting sugar 75 mgm.; after 50 grm. glucose, 137; 177; 147; 133; 123 mgm. at half-hourly intervals respectively.

Treatment.—The patient was given 60 c.c. cortin on the first day, followed by 20 c.c. daily thereafter. Her general condition improved, the blood-urea fell to 25 mgm., and she was ultimately discharged on December 15, 1937. She continued to have 5 c.c. cortin daily until February 1938, when the dose was gradually increased to 20 c.c. cortin daily as she did not maintain her improvement on lesser amounts, and still complained of some attacks of nausea, occasional vomiting, and feeling of weakness. She could not tolerate salt orally.

Case 26.—A male journalist, aged 52, had a partial gastrectomy in 1935 for gastric and duodenal ulcers, a number of calcified glands being removed from the mesentery at a later date. In October 1937 he was admitted on account of increasing pigmentation of the skin (which began in 1936), nausea, vomiting, abdominal pain, marked asthenia, and loss of weight.

On examination.—Fairly slim, had lost much weight. He had a generalized dark brown pigmentation over the whole body although the knees, elbows, knuckles, and axillæ, were a little less pigmented, while the buccal mucosæ showed patchy pigmentation. He had grey hair, brown eyes, moist tongue, no enlargement of tonsils or glands. Blood-pressure 106/70; temperature 97° F.; pulse 80, regular, fair volume; weight 8 st. The lungs, nervous system, and heart, were apparently normal; there was some generalized diffuse tenderness of the abdomen but nothing abnormal was felt.

Urine: Specific gravity 1025; acid reaction; no abnormal constituents. Urinary chloride excretion was 6–7 grm. daily. Blood-urea 77 mgm.; sugar 70; chlorides 450; sodium 318; phosphate 6·3 mgm. per 100 c.c. X-ray showed no evidence of pulmonary disease; there was an old resection of left 10th rib; there was no calcification seen in suprarenals or kidneys, but calcified abdominal glands were visible.

Blood-count: R.B.C. 4,200,000; Hb. 47%; W.B.C. 7,500; polys. 74·5; lymphos. 18; large monos. 4·5; eosinos. 3·0; basophils nil %. No abnormal cells and platelets were abundant. He had hypochlorhydria gastrica, and a negative Wassermann reaction. Glucose tolerance test—fasting blood-sugar 41 mgm.%; after 50 grm. glucose 95; 113; 67; 47; 37 mgm. respectively at half-hourly intervals.

Treatment.—He was given 20 c.c. cortin daily intramuscularly, later 15 c.c., and then 10 c.c. daily, with considerable improvement and rapid relief from the nausea and vomiting. He gradually lost his symptoms, appetite improved, his weight increased, and he was finally discharged with a blood-pressure of 125/80. He was tried several times with increased salt in his diet, but was unable to tolerate it, and certainly did not take very much after discharge from hospital. The hypochromic anæmia was treated with different preparations of iron which he did not tolerate too well. He was given 5 c.c. cortin on alternate days on his return home (February 1938) but this was increased to 5 c.c. daily as he did not seem to maintain sufficiently good progress. In June his blood-pressure was 146/80 and he was very well although he was still unable to take salt or much iron. He returned to work but could not reduce the cortin to less than 5 c.c. on alternate days without feeling its loss. In July 1938, his blood-pressure was 148/90 and the blood-count rose to: R.B.C. 4,970,000; Hb. 93%; W.B.C. 15,000; polys. 74·5; lymphos. 20; large monos. 3; eosinos. 2; basos. 0·5%; abundant platelets; no abnormal cells or other features.

At this time he began to complain of pain in the right hypochondrium in recurrent attacks with some vomiting; as this did not subside he was readmitted to hospital for further investigation—his blood-urea was 78 mgm., blood-pressure 150/100; urine, specific gravity 1020; acid reaction, no albumin, sugar, acetone, or casts. X-ray examination did not show any alteration or delay in the alimentary tract. Occult blood test of fæces was negative. He was given symptomatic treatment and 2·5 c.c. of cortin daily with considerable improvement. The blood-urea fell to 42 mgm. in three weeks, and his symptoms subsided. His weight was 8 st. 10¾ lb. He was discharged on September 24, 1938, on 2·5 c.c. cortin on alternate days.

Results of Cortin Therapy

Dosage.—Both intravenous and intramuscular routes were effective, but the former was easier and pleasanter when the larger doses were given in single injections. Better results with a " smoother " clinical improvement were obtained by giving the larger daily amounts in three or four divided doses spread over the twenty-four hours. I have never had or seen in my patients any reactions that could be attributed to the injections of the modern preparations of cortin. Very large daily doses of cortin such as 60–100 c.c. may be needed in some cases, and may be required continuously for days or even weeks before clinical improvement is sufficient to permit a reduction in dose. Consequently the cost of treatment may be heavy. Nevertheless, once clinical improvement commences and the blood-urea falls to normal limits the reduction in dosage is usually very rapid until the maintenance dose is reached ; this may be quite small, and with the use of salt I have found that some cases can discontinue cortin for long periods, in one case as long as four years. The total amounts of cortin required to bring patients to maintenance levels have varied between 65 c.c. and 6·06 litres, but in view of the long-term results we are undoubtedly justified in pushing the treatment. Sudden crises may occur in these patients, sometimes spontaneously, but frequently after severe infections such as colds and influenza. In these cases prompt measures are required.

Pyrexia.—Temperature in these patients requires some comment. I have noted that certain patients during the course of treatment will display variable degrees of pyrexia, sometimes slight, sometimes marked hyperpyrexia, the latter usually occurring in the last few days of life. If these periods correspond with injections of cortin or desoxycorticosterone acetate the latter may be suspected of causing reactions. In my experience these febrile cases are almost always tuberculous, and autopsy shows tuberculous masses in the suprarenal residues. Prognosis in these cases is bad, even very large doses of cortin will ultimately fail to produce remissions.

Improvement in symptoms.—In the patients responding to cortin therapy there has been excellent improvement in symptoms—general asthenia, muscular weakness, exhaustion, apathy, all disappeared rapidly, and were followed by remarkable improvement in mental outlook. Gastro-intestinal symptoms were also relieved very quickly, appetite returned, weight increased and blood chemistry and temperature became normal.

Pigmentation certainly showed improvement, and in my long-standing patients the dark brown colour disappeared, especially from the mucous membranes, although there was usually some persistence of a generalized very light brown colour in the skin. Blood-pressure may increase to a variable degree, the majority showing a systolic blood-pressure of 100–130.

Desoxycorticosterone

The main disadvantages of the natural suprarenal cortical extracts are difficulty of preparation, standardization, and cost. The isolation and synthesis of the pure hormone would therefore be advantageous. I have given the synthetic desoxycorticosterone acetate (Steiger and Reichstein) dissolved in vegetable oil (5 mgm. per c.c.) to four cases of uncomplicated classical Addison's disease.

Dosage.—The dosage of desoxycorticosterone acetate was unknown in the beginning. Animal tests had suggested that 5 mgm. should be equal to about 40 c.c. cortin, and 5–10 mgm. proved to be a satisfactory initial dose.

In Table IV I have summarized my results.

TABLE IV.—ADDISON'S DISEASE TREATED WITH DESOXYCORTICOSTERONE ACETATE.

Case	Sex	Age	Total DOCA (mgm.)*	Maximum daily dose (mgm.)	Present maintenance dose (mgm.)	Present condition
23	M.	35	115	5	5 weekly	V. good
27	F.	56	300	15	—	Dead (Tb.)
28	F.	56	272·5	10	5 weekly	V. good
29	M.	36	202·5	5	5 weekly	V. good

* To December 8, 1938.

Case 23 (*see* Case 23 described above and Tables II, IV and V) was an old patient whose needs in terms of cortin were well known. At the time that desoxycorticosterone acetate was being used, this patient had shown a sudden relapse after his minimum daily maintenance dose of 20 c.c. cortin had been reduced to 10–15 c.c. On admission he was very drowsy, and complained of muscular fatigue, loss of appetite, tiredness, nausea, and vomiting, some loss of weight.

On examination.—The pigmentation had increased slightly. His weight had fallen again to 7 st. 13 lb. Blood-pressure 80/65; pulse 75, regular, moderate volume. Other findings were similar to those when he was in hospital previously.

Urine: Specific gravity 1018; acid reaction; no abnormal constituents. Blood-urea, 50; sugar 85; sodium 296; chlorides 398; potassium 26 mgm./100 c.c.

Treatment.—The patient was given the same diet he had been taking at home, but cortin was replaced by desoxycorticosterone acetate (October 12), 5 mgm. daily intramuscularly, and within a few days he felt much better, the blood-urea fell to half, and all nausea and vomiting had ceased. After eight days the dose was reduced to 5 mgm. on alternate days for eleven days, then to once every third day until he was discharged from hospital on November 24, 1938. He is now having 5 mgm. weekly instead of 20 c.c. cortin daily.

Within the first week of receiving desoxycorticosterone acetate he said very definitely that he felt much better after 5 mgm. than he did after 30 c.c. of cortin, especially in that the following morning he felt fit and well on rising. His response to the small doses was excellent in all respects, and weight increased steadily. In this case 5 mgm. desoxycorticosterone acetate produced effects equal to at least 30 c.c. of cortin. On December 12, 1938, his blood-pressure was 110/78 and weight 8 st. 8 lb., and he feels very well indeed (Table V).

TABLE V.—CASE 23.

Date	Blood-pressure	Treatment DOCA (mgm.)	Weight	Urea	Chloride	Sodium	Potassium	Sugar
12.10.38	80/65	5 daily		50	398	296	26	81
13.10.38	80/60	5 daily	7 st. 13 lb.					
21.10.38	90/55	5 alt. days		24				
29.10.38	95/55	5 every		25				
18.11.38	90/60	3rd day	8 st. 2½ lb.	24	465	330	20	109
12.12.38	110/78	5 weekly	8 st. 9 lb.	22				

Case 27.—A housekeeper, aged 36, admitted September 14, 1938.

Four months previously she had noticed that the skin was becoming pigmented with increasing rapidity, associated with dryness and pruritus. This was associated with a recurrent nausea after each meal. She began to feel weak and tired much more easily than previously; dizziness occurred with change of posture.

In August she began to vomit mainly after meals, but this was temporarily relieved by rest in bed, recurring when she got up. For the last two weeks vomiting persisted even when resting. Constipation became marked with the onset of vomiting.

She lost her appetite for food and had lost at least 1½ st. in weight in the previous twelve months. There was no complaint of indigestion but abdominal distension followed the taking of food. She slept well and did not complain of pain, dyspnœa, palpitation, œdema, cough, paræsthesiæ, or night-sweats. The menopause was completed three years previously.

Previous medical history.—No history of similar previous attacks, but in 1921 she had tuberculosis of the left ankle which was in plaster for three and a half years, and in 1936 she was in a convalescent hospital for nine weeks for ? debility.

There was nothing relevant in the family history.

On examination.—The patient was very drowsy, although mentally she appeared normal. She had a very dark brown pigmentation of the skin with dryness and peeling of superficial layers in parts. The brown colour was very dark on the neck, hands (knuckles), elbows, groins, axillæ, knees, and toes. There were dark pigmented areas in the vaginal and buccal mucous membrane, palate, sides of the tongue, and lips. The nipples were not specially pigmented. The skin was very inelastic. Conjunctivæ very pale. The patient was very thin; weight 8 st. 6 lb.; temperature 98° F.; blood-pressure 100/80 (next day 85/75); pulse 120, very feeble, barely palpable. No glandular enlargements. No definite abnormalities were detected in the heart, lungs, abdomen, or nervous system.

Urine: Specific gravity 1014; acid reaction; trace of albumin, no acetone or sugar. Daily chloride excretion was 1·33 grm.

Blood-count: R.B.C. 4,460,000; Hb. 84%; W.B.C. 18,100; polys. 82·5; lymphos. 12·0; large monos. 5·0; eosinos. 0·5; basos. nil %. Aniso- and poikilocytosis slight; nucleated red cells nil; platelets abundant.

Blood-sugar 77 mgm.; blood-urea 110 mgm.; sodium 282 mgm.; chlorides 412 mgm.; potassium 25 mgm./100 c.c. She had achlorhydria gastrica, a negative Wassermann reaction, and a basal metabolic rate of −1%. Radiograms of chest and loins were normal.

Treatment.—The patient was given 12 mgm. desoxycorticosterone acetate intramuscularly daily for two days, then 18 mgm. on the third and fourth days in divided doses of 6 mgm. each.

She showed marked improvement, vomiting ceased, and the dose was reduced to 5 mgm. daily for five days and to 2·5 mgm. daily for eight days (Table VI).

TABLE VI.—CASE 27.

Date	Blood-pressure	Treatment DOCA (mgm.)	Urea	Chloride	Sodium	Potassium
14.9.38	100/80	12	110	412	282	26
15.9.38	90/75	12				
16.9.38	85/75	12				
17.9.38	95/75	18	114	408	280	
18.9.38	95/75	5 daily				
22.9.38	100/90	2·5 daily	46	456	320	
30.9.38	100/85	5 daily	30			
11.10.38	115/95	5 daily	26	485	332	
18.10.38	100/90	5 alt. days	32	476		
29.10.38	115/90	5 daily	26	452	330	20
12.11.38	115/90	18	20	454	330	
13.11.38	115/85	18	36			
14.11.38	115/85	18				

The blood-urea fell rapidly and her general condition improved further. She still showed a disinclination to sit up in bed and her appetite was only fair, although the weight increased slightly. The desoxycorticosterone acetate was continued in doses of 5 mgm. daily for nineteen days, and on alternate days thereafter until October 30 (eleven days), when it was again given daily. She was given at this stage 10 grm. salt daily orally, but she did not tolerate it very well. Although the blood chemistry remained within normal limits, the weight now began to fall slightly, the patient felt more tired and limp, and her temperature showed more marked variations, hyperpyrexia (103°) developing a few days later. She failed to respond to increased amount of desoxycorticosterone acetate and died November 14, 1938.

Autopsy (Dr. Susman): Showed both suprarenal glands (right 6·5 by 3 by 1 cm.; left, 5·5 by 3·2 cm.) were completely disorganized and of firm consistency, very much enlarged and thickened, caseous, and on cutting extruded purulent material. There was nothing else of note.

Case 28.—A female winder, aged 56, was admitted to hospital complaining of general lassitude, weakness, and increasing pigmentation of the skin.

She was well until two years previously, when she noticed that she soon became tired on exertion. During the last twelve months the lack of energy has prevented her from working, the pigmentation has increased, and she has lost weight. She had nausea and slight vomiting prior to admission on 17.9.38 and was constipated. There was nothing relevant in her previous medical or family histories.

On examination.—Showed a thin, emaciated, very deeply pigmented woman; mentally fairly good although slightly slow in answering. The skin was a generalized coffee colour being much darker (almost black) on the neck, knees, elbows, and knuckles. The nipples were very dark, and there were pigmented patches in the mouth, on the sides of the tongue, gums, and vagina. The skin was smooth. There were no enlarged glands; the tongue was clean and moist, tonsils normal; jaws edentulous. Pulse 80, regular, poor volume; blood-pressure 105/70; temperature 97·6° F. Weight 7 st. 2 lb. There was nothing abnormal in the heart, lungs, abdomen, or nervous system.

Urine: Specific gravity 1020; acid reaction; no sugar, acetone or albumin. Blood-urea 22 mgm.; sodium 334 mgm.; chlorides 456 mgm.; potassium 22 mgm.; cholesterol 185 mgm./100 c.c. of blood. Urinary chlorides—averaged 3·5 grm. NaCl daily.

Her basal metabolic rate was −1% and she had achlorhydria gastrica and a negative Wassermann.

Glucose tolerance test: Fasting sugar 73 mgm.; after 50 grm. glucose 118; 148; 118; 95; 81 mgm.% at half-hourly intervals respectively.

Radiograms of chest—4.10.38: "In left upper lobe there is a triangular area of infiltrated

lung, probably tuberculous disease." 30.11.38: "There was good diaphragmatic movement on respiration. No evidence of cardiac enlargement. Some increase in pulmonary vascular markings. The triangular area previously described does not show. There is a faint mottled shadow in the left infraclavicular region. Films taken in lordosis do not show any other abnormalities. Probably healing."

Radiogram of loins: "No calcification. Calcification of costal cartilage."

Treatment.—2·5 mgm. desoxycorticosterone acetate daily for five days; then increased to 5 mgm. and later 10 mgm. daily for eleven days; she showed a good clinical reponse, felt better in every way, and put on a few pounds in weight. The desoxycorticosterone acetate was reduced to 5 mgm. for seven days, then was given on alternate days for twenty-six days, and finally 5 mgm. twice weekly as her clinical condition continued to improve (Table VII). She was discharged on 5 mgm. desoxycorticosterone acetate weekly. On December 12, 1938, she was very well, blood-pressure 100/70; weight 7 st. 9 lb.

TABLE VII.—CASE 28.

Date	Blood-pressure	Treatment DOCA (mgm).	Weight	Urea	Chloride	Sodium	Potassium
17.9.38	120/70		7 st. 12 lb.	22			
24.9.38	105/70	2·5 daily	7 st. 0 lb.	24	456	326	21
29.9.38	80/55	5·0 daily	6 st. 12 lb.	24	464	325	22
2.10.38	98/65	10 daily		24			
13.10.38	98/65	5·0 daily	7 st. 6 lb.	24	490	334	22
18.10.38	100/68	5·0 alt. days		22	482	334	22
29.10.38	105/80	5·0 every 3rd day	7 st. 3 lb.	24			
16.11.38	102/68	5·0 alt. days	7 st. 3 lb.	22			
28.11.38	108/70	5·0 every 3rd day	7 st. 4 lb.	18	470	334	20
12.12.38	100/70	5·0 weekly	7 st. 9 lb.				

Case 29.—A cotton operative aged 36, complained of weakness, loss of energy, dyspnœa on exertion, loss of 2½ st. in weight, nausea, and soreness of the tongue for six months prior to admission to hospital. He had also noticed a gradual darkening of his skin during that period.

On examination.—A brownish-coloured emaciated man; asthenia moderate, tongue clean, moist; slight glossitis; lower teeth good, had upper dentures; slightly congested tonsils; no enlarged glands; weight 7 st. 8 lb.; temperature 97·6° F.; pulse 96, regular, poor volume; blood-pressure 88/72.

The skin was a light brown colour, more marked on the elbows, knuckles, face, abdomen; the buccal mucous membrane was also pigmented. No abnormalities were found in the heart, lungs, abdomen, or nervous system. He had achlorhydria gastrica, a negative Wassermann, normal basal metabolic rate, normal van den Bergh reaction, normal red cell fragilities, increased glucose tolerance.

Blood-count: R.B.C. 3,690,000; Hb. 68%; W.B.C. 4,400; normal differential white cell count. Radiograms of chest and loins—did not show any evidence of tuberculosis or calcification, but the heart was very small.

Blood-urea 38, sugar 80, chlorides 460, sodium 325 potassium 22 mgm./100 c.c. Urine was normal; urinary chloride excretion was less than 8 grm. daily.

TABLE VIII.—CASE 29.

Date	Blood-pressure	Treatment DOCA (mgm.)	Weight	Urea	Chloride	Sodium	Potassium
18.9.38	94/72		7 st. 8 lb.	38	460	325	22
24.9.38	85/60	2·5 daily	7 st. 5 lb.	44			
29.9.38	78/60	5·0 daily					
9.10.38	90/65	5·0 daily	7 st. 5 lb.	24	460	326	20
20.10.38	88/58	5·0 alt. days	7 st. 7 lb.	30	478	334	18
30.10.38	95/80	5·0 alt. days + Potassium-free diet	7 st. 7 lb.	28	470	330	18
1.12.38	98/75	5·0 twice weekly + Potassium-free diet	8 st. 1 lb.				

Treatment.—Kept under observation without treatment for a week, during which time his blood-urea increased slightly to 44 mgm. and his weight fell to 7 st. 5 lb., then given 2·5 mgm. and later 5 mgm. desoxycorticosterone acetate daily with definite improvement in his clinical condition, and blood-urea (Table VIII). On October 30 his blood-pressure was 95/80 and he had

then been having 5 mgm. on alternate days for ten days, blood chemistry was normal, and he felt much better. Continuing with 5 mgm. desoxycorticosterone acetate on alternate days, he was given a diet poor in potassium and although his weight increased a little more and his serum potassium fell very slightly, his clinical condition did not show any marked improvement that could be ascribed to the diet. He was discharged from hospital on December 9 feeling quite well—blood-pressure 98/75, weight 8 st., and normal blood chemistry.

Results of treatment with desoxycorticosterone acetate.—These four cases observed for a relatively short period only allow me to say tentatively that as far as my experience goes desoxycorticosterone acetate appears able to replace cortin to a considerable degree, but we do not know what the long-distance effects will be.

Subject to much further investigation 5 mgm. of desoxycorticosterone acetate is probably, in the initial stages, equivalent to not less than 15–30 c.c. cortin (cp. Case 23).

I have had no reactions after its use, nor have any of the patients developed or complained of lumps or pain at the sites of injection. The small 1 c.c. injections are much preferred to the more bulky doses of cortin.

Salt therapy.—I have tried the use of salt, or salt mixtures (such as sodium citrate or bicarbonate with salt), alone and in association with cortical hormone therapy, with the following results :—

(*a*) In severe and moderately severe cases of Addison's disease salt is of little value in initiating remissions.

(*b*) In some mild cases, however, salt alone may be of value.

(*c*) After crises have been relieved, or severe cases have been started well on the way to recovery and gastro-intestinal symptoms, especially nausea and vomiting, have been relieved by the use of suprarenal cortical hormone, then salt is of very great value. It usually enables the cortin to be reduced considerably and rapidly.

(*d*) Salt apparently acts as a good maintenance therapy in some cases and I have four patients who, after preliminary treatment with cortin, have only been on salt therapy for periods of between one and four years (*see* Table I).

(*e*) There are occasional patients who cannot tolerate the salt in any amount.

Diets poor in potassium.—The observation that in Addison's disease there is not only a sodium chloride loss, but also a potassium retention, led to the suggestion by Wilder and others that a potassium-poor diet should be employed in the treatment of Addison's disease—since a reduced intake of potassium reduced the body's need of sodium. It is neither easy to assess such a form of treatment, nor to devise a convenient and satisfactory diet sufficiently deficient in potassium (i.e. less than 1·5 grm.). Such diets are grossly deficient in other essentials.

Following the suggestions of Wilder, I have tried the potassium-poor diet on three patients. In drawing up such a diet the choice of bread and cereals must be restricted, the amounts of milk, fruit, meat, and vegetables must be diminished, while meat and vegetables must be cooked in such a manner that the mineral salts are removed. Soups, gravy, meat extracts, sauces, condiments (except salt), dried fruit and vegetables, chocolate, &c., are forbidden. A typical daily menu I have used is :—

POTASSIUM-REDUCED DIET.

Breakfast	*Dinner*
1 egg	3 oz. stewed beef
½ oz. butter	3 oz. potatoes
2 oz. white bread	4 oz. root vegetables
½ oz. cream (tea)	3 oz. tinned pears or apples
Marmalade	1 oz. cream
Tea	*Supper*
1 oz. white bread	2 oz. white bread
¼ oz. butter	1 oz. cheese
1 oz. honey	½ oz. butter
½ oz. cream (tea)	½ oz. cream (tea or coffee)
Sweet biscuits	

Potassium 0·8 *grm.* Protein 57 grm. Calories 2,000.

The vegetables and meat are boiled in a large excess of water or several changes of water are used with advantage ; this removes most of the mineral salts.

This diet is said to contain about 0·8 grm. potassium, 57 grm. protein, and has a value of 2,000 calories.

The diet is probably deficient in vitamins B and G, calcium, phosphates, iron, and other minerals, and these should be given therapeutically.

It is obvious that a diet poor in potassium is not going to be convenient or particularly cheap for many patients at home, and my experience is that the results are not sufficiently valuable to justify its use, unless modified to reduce the potassium intake more moderately.

Of the three patients to whom I gave this diet, the first case did not show any response and cortin had to be given as she was getting steadily worse, while the other two cases were put on to the diet after they had responded well to desoxycorticosterone acetate. I was unable to convince myself that they benefited by it.

Summary

(1) Natural suprarenal cortical extracts are of very definite value in the treatment of Addison's disease, provided that sufficiently large doses are given. In my experience they have been free from unpleasant reactions.

(2) Of 13 patients treated with cortical extracts, four have died and nine are very well after periods of twelve months to four years eight months. Four of these latter have had no cortin for periods of twelve months to four years, but still take extra salt in their diets.

(3) Synthetic desoxycorticosterone acetate appears to act in a similar manner to the natural extract in initial doses of 5–10 mgm. daily. The maintenance doses for long-term effects are probably considerably less, but it is too soon to assess this accurately—three cases are taking 5 mgm. weekly as maintenance doses, and one case died from the tuberculous process.

(4) Apparently 1 mgm. desoxycorticosterone acetate is equivalent to at least 3–6 c.c. natural cortin, and may vary in different patients.

(5) Using either the natural or the synthetic cortical hormone the asthenia, muscular weakness, nausea, vomiting, are rapidly relieved, appetite returns, weight increases, and the pigmentation becomes less marked. The blood chemistry returns to normal.

(6) Blood-pressure gradually increases, but usually remains a little subnormal, body temperature approaches the normal range (except when active tuberculous processes are present—pyrexia suggesting a bad prognosis).

(7) The use of salt alone is insufficient in most cases to relieve the condition, especially in crises, and usually exaggerates the nausea and vomiting when present. Given in association with the cortical hormone salt is of considerable benefit, permitting a much more rapid reduction of dosage, and apparently will maintain some cases in good health without the continuation of cortin therapy.

(8) Diets poor in potassium do not appear to be of great value in the more severe cases, and are inconvenient for many patients at home.

Most of these investigations have been carried out for the Therapeutic Trials Committee of the Medical Research Council, and I am very grateful to Messrs. Organon Laboratories for the generous supplies of active cortin and desoxycorticosterone acetate, and also to Messrs. Ciba Ltd. for supplies of the latter.

POSTSCRIPT (April 3, 1939).—The cases reported in Table I are still very well as indicated. Of those receiving desoxycorticosterone acetate, after a further four months, cases 23 and 28 are very well on 5 mgm. twice weekly, while case 29 and two further cases only require 5 mgm. once weekly.—J. F. W.

Dr. H. P. Himsworth: The efficacy in general of the modern treatment of Addison's disease being now established, attention may be turned to the particular value and limitations of some of the therapeutic agents employed, and of these I wish to draw attention to certain points in relation to the low potassium diet, the use of sodium chloride, extracts of the suprarenal cortex, and the synthetic preparation, desoxycorticosterone acetate.

The low potassium diet has been strongly advocated in America. My experience of its use is small, and I have not been impressed by its value. There are few human beings who can tolerate it for any length of time. I would add, however, that although I doubt the practical value of a low potassium diet, I am quite convinced of the deleterious effect of a high potassium intake in cases of Addison's disease. For that reason foods with a high potassium content, such as meat, pulses, and nuts, should be restricted.

The value of sodium chloride as an adjuvant to cortical extracts is accepted, but I think it possible that it has more than an adjuvant action. A young girl aged 17 with Addison's disease was given a diet in which the salt intake was maintained approximately constant at the normal figure of 4 grm. daily. She was given cortical extracts in sufficient doses to produce normal values of sodium and urea in the blood. For the period of six weeks that she was thus treated the systolic blood-pressure oscillated around 95 mm. of mercury and the diastolic round about 55 mm. 20 grm. of salt were then given each day, in addition to the previous treatment, and both the systolic and the diastolic blood-pressures rose and were maintained 15 mm. higher. This patient also illustrates another point in connexion with the blood-pressure. When cases of Addison's disease first come under observation the pulse-pressure is low, often only 10 or 15 mm. of mercury. As the disease is brought under control the pulse-pressure steadily increases until it reaches normal values.

The cortical extract of which I have had most experience is cortin (Organon), and it has proved very reliable. One misfortune has occurred with it. On one patient it produced fatal anaphylaxis. The patient, a woman aged 33, had been treated for Addison's disease with 20 grm. of sodium chloride daily and 5 c.c. of cortin twice a week. Under this treatment she felt fairly well and was able to do her own housework. Ten days before her final admission she used up her supply of cortin and deferred obtaining more. The day before admission she contracted the prevailing influenza, and next morning was found unconscious. On admission it was difficult at any moment to be sure that she was still alive. The breathing was intermittent and shallow, the pulse imperceptible, the extremities cold, and the blood-pressure could not be estimated. 80 c.c. of cortin were given intravenously at once and then a slow glucose saline intravenous infusion was started. Four hours later she was fully conscious and the blood-pressure was 70 mm. Three hours after this she began to breathe with difficulty, rapidly passed into status asthmaticus, and died eight hours later. At autopsy the blood in the vessels was fluid, and the lungs were so distended that after removal of the sternum they ballooned out of the thorax. Examination of the suprarenal glands showed atrophy.

As an example of what may be achieved in the relief of Addison's disease by means of cortin and sodium chloride I may quote the following case :—

The patient, a man aged 34, developed Addison's disease acutely two years ago. His case proved to be of exceptional severity in that it was found impossible to maintain him on less than 25 c.c. of cortin daily even though he was taking 20 grm. of salt in addition. But on such a dose for the last eighteen months he has been remarkably well. He can drive 200 miles a day by car, in Switzerland he was able to ski and climb 3,000 ft. up an easy mountain, and he has recently held a responsible if not arduous post of daily routine work. His clinical condition is not, however, uniformly stable at this relatively high level and is always liable to remissions as a result of mild infections. On the whole he is capable of living a quiet life and his appetite is sufficiently good to permit him indulging an interest in the table. This patient has found that his own subjective feelings of health are better guides to treatment than a knowledge of the behaviour of his blood

electrolytes. If his appetite is not good he increases the dose of cortin ; when he feels well again he gradually reduces the dose to his usual level of 25 c.c.

The recent introduction of the synthetic preparation, desoxycorticosterone acetate, has raised hopes that the bulk and frequency of the intramuscular injections would be reduced and expense of treatment curtailed. Through the courtesy of Messrs. Ciba I have been able to test this new preparation on two cases of Addison's disease, the man described above and another case. In each case the general plan of the test was the same ; the patient was given cortin until the blood chemistry and general condition was satisfactory, and then desoxycorticosterone acetate was substituted for the cortin. In both cases the sequence of events was the same. Within a few days of starting the decoxycorticosterone the patient began to feel stronger, and a further improvement in the blood chemistry occurred. This favourable state continued for two or three weeks and then weakness began to appear, and within a few days the patient clinically appeared to have relapsed. But here a peculiar point emerged ; despite the clinical relapse the blood-urea and the plasma sodium levels remained normal.

In the case of the man whose favourable progress under cortin has been described, we had the advantage of having studied the patient for the two previous years, and it was known that 25 c.c. of cortin and 20 grm. of sodium chloride were required by him each day. In view of the large cortin requirement the patient was first given 20 mgm. of desoxycorticosterone acetate intramuscularly each day. The daily intake of 20 grm. of sodium chloride was continued throughout the period of observation. Within three or four days the patient began to feel much stronger, the blood-pressure rose from 110 mm.Hg to about 120 mm., the blood-urea fell from 52 mgm./100 c.c., about which level it had remained for the previous six months, to 32 mgm./100 c.c., and the plasma sodium rose from 320 mgm./100 c.c. to 350 mgm./100 c.c. The patient was so impressed by his improved health that, despite the irritating lumps which formed at the site of the intramuscular injection, he chose to continue using the new preparation. After two and a half weeks on 20 mgm. of desoxycorticosterone daily it was thought permissible to reduce the daily dose to 15 mgm. Five days later the patient began to feel less strong and his appetite began to fail, so the dose was again increased to 20 mgm. daily. Despite this increase during the next week his condition steadily deteriorated, and marked weakness and anorexia developed. But his blood-pressure did not fall, his blood-urea remained between 36 and 25 mgm./100 c.c., and the plasma sodium at its previous high level of 350 mgm./100 c.c. It was soon evident that the increased dose of new synthetic preparation was not effecting an improvement, and daily injections of 30 c.c. of cortin were substituted. Improvement gradually followed, and a fortnight later the patient had returned to his usual level of health. In this fortnight the blood-urea rose from 25 mgm. 100 c.c. to 40 mgm./100 c.c., and the plasma sodium fell slightly from 350 mgm./100 c.c. to 330 mgm./100 c.c. The plasma potassium was not measured.

The second case was a girl aged 17 who had not previously received treatment for Addison's disease. As it was wished to estimate the potency of desoxycorticosterone relative to cortin no extra sodium chloride was given, but the patient was given a diet containing a constant normal amount of sodium chloride. At the commencement of treatment the blood-urea was 107 mgm./100 c.c. and the plasma sodium 295 mgm./100 c.c., and it was found necessary to give 20 c.c. of cortin daily to reduce the blood-urea to 45 mgm./100 c.c. and to raise the plasma sodium to between 310 and 330 mgm./100 c.c. After three weeks 5 mgm. of desoxycorticosterone was substituted for the cortin. Within a few days the patient felt better, the blood-urea sank to 36 mgm./100 c.c., but the plasma sodium remained about 320 mgm./100 c.c. The clinical improvement was so marked that sixteen days later the dose of the synthetic preparation was reduced to 5 mgm. on alternate days. Six days later the patient said she did not feel so well, and during the next five days she passed into a condition clinically typical of an acute relapse. The appetite disappeared and, although she vomited only twice, nausea was present. Pain developed in both flanks, the pulse-rate rose to 140, and on the last two days the temperature began to rise and the blood-pressure fell to 70 mm.Hg. The patient was now desperately ill, pale and anxiously restless. But, as in the other case, the blood-urea remained within reasonable limits at 45 mgm./100 c.c. and the plasma sodium at 315 mgm./100 c.c. Other changes in the chemistry of the body more compatible with an Addisonian crisis had, however, occurred. Ketonuria was marked, and the blood-sugar was at the low level of 53 mgm./100 c.c. At this stage intravenous glucose saline was

given and 50 c.c. of cortin intramuscularly. Thereafter she was given 50 c.c. of cortin and later 20 grm. of sodium chloride daily, and she slowly recovered.

It will have been noted that in each case the relapse followed a few days after the dose of desoxycorticosterone had been reduced. That the relapse was not due to underdosage is indicated by, firstly that in the male case subsequent increase of dosage did not improve the clinical condition, and secondly that in both cases there was no significant change in either the blood-urea or plasma sodium such as is known to occur when the supply of cortical hormone is deficient.

The similar sequence of events in both these cases suggests that in each it should be ascribed to the one common factor, the desoxycorticosterone acetate preparation. but before endorsing this suggestion the possibility of interfering factors must be considered. It is well recognized that intercurrent infection in the patient detracts from the efficacy of preparations of the suprarenal cortex. Both cases in which the new preparation was tried were probably of tuberculous origin—one had had a nephrectomy for tuberculosis of the kidney, the other had calcified suprarenal glands. The male case showed no clinical evidence of intercurrent infection, and the sedimentation rate remained unchanged at 12 mm. per hour. The female patient had coli bacilluria during the initial period of treatment with cortin, and the urine was cleared with calcium mandelate. After, but not during, the relapse bacilli again appeared in the urine. I do not feel that this evidence indicates that intercurrent infection brought about the relapse in these two cases. It has been suggested to me that the relapses might have been due either to deficiency of vitamin B or overdosage with the synthetic preparation. The man was taking a vitamin-B concentrate throughout the test period and the dietitian assures me that the female case was receiving an adequate supply of vitamin B. The suggestion of overdosage can be refuted in the case of the man. In his case overdosage with cortin is associated with an increase in libido. This did not occur during the period in which he was treated with desoxycorticosterone acetate.

I, therefore, suggest that the evidence of these two cases indicates that the relapses were associated with the use of desoxycorticosterone acetate, and in this opinion I am fortified by the similar but independent experience of Dr. Avery Jones. Whether the relapse is due to a direct toxic action of the preparation, or whether it is due to the absence of some factor from the synthetic preparation which is present in extracts of the suprarenal cortex, I cannot say, but in view of the initial improvement which follows the administration of desoxycorticosterone acetate I incline to the latter view. It would appear that, whilst cortin is reliable and almost free from danger, desoxycorticosterone acetate is not yet sufficiently satisfactory for general use.

Dr. Avery Jones: *Desoxycorticosterone acetate in Addison's disease.*—I wish to discuss briefly my experience with desoxycorticosterone acetate in two cases of Addison's disease. The preparation was kindly supplied by Messrs. Ciba Ltd.

Case 1.—Female, aged 45, admitted three years ago to the Medical Professorial Unit, St. Bartholomew's Hospital, with a six-months' history of increasing lassitude, anorexia, vomiting and darkening of the skin.

On admission, she was a pale woman with pigmentation well marked over pressure points and in the oral mucosa. In addition, there were numerous pigmented spots in the face, limbs, and trunk. Blood-pressure was 84/60, blood-urea 92 mgm.%, serum sodium 285 mgm.%, hæmoglobin 110%. X-ray showed no calcification of the suprarenal regions. Temperature tended to be subnormal.

She was given 9 grm. sodium chloride and 3 grm. sodium citrate daily. After three weeks the blood chemistry had returned to normal (Hb. 90%, blood-urea 38 mgm.%, serum sodium 327 mgm.%). The systolic blood-pressure was still below 90 mm.Hg and there was little, if any, improvement on salt alone.

She was then given 10 c.c. of cortin daily intramuscularly. The improvement after one week was striking, the increase in vitality and vivacity being most marked. The systolic blood-pressure slowly increased to 110 mm.Hg.

She went home having 10 c.c. of cortin and 12 grm. sodium chloride with 4 grm. sodium bicarbonate daily, but was unable to be up for more than six hours a day.

Two years ago she was readmitted and the cortin was stopped. After a few days there was increasing lassitude. On the sixth day, she was inadvertently given a dose of senna. The bowels were opened five times. The same evening the temperature rose to 104° F., the blood-pressure fell to 80. She became comatose, and was critically ill for five days. She was given sodium chloride intravenously and 40–90 c.c. cortin daily. This saved her from a stormy bout of acute adrenal insufficiency.

After this she continued at home with 10 c.c. cortin daily and the same dosage of sodium salts. She was able to get up only one to two hours a day. Economic considerations prevented her from having a larger dose of cortin. During this time she had one febrile attack only, lasting a few days. Her throat was sore and she suffered from considerable malaise, but recovered rapidly without increasing the dose of cortin.

She was readmitted three months ago for a therapeutic trial of desoxycorticosterone acetate. During the whole time she received the same dose of sodium salts as previously. After a control period of ten days, she was given 5 mgm. daily of desoxycorticosterone acetate. She did not feel as well as usual; she slept poorly at night and was troubled with bad dreams, a symptom prominent before cortin was begun originally. After seven days the dose was increased to 10 mgm daily and she improved considerably. She remained very well for eighteen days and was able to get up for three to four hours a day. Towards the end of this period, however, she had disturbed nights again.

The blood-pressure had risen slightly, but suddenly she became very weak and her temperature rose to 102° F. Next day the temperature was down to 99° F., but an extensive herpes simplex appeared on the lips. The blood-pressure remained over 130, and for this reason the desoxycorticosterone was continued. On the sixth day the blood-pressure fell to 110, she became drowsy, and although her blood-urea was only 23 mgm., it seemed as though she were passing into a state of acute adrenal insufficiency. She was given 100 c.c. of cortin that night, and next day she said she had never felt better in her life! The desoxycorticosterone acetate was continued for four days, but fever persisted and she was changed over to cortin, 30 c.c. daily. Her temperature settled down, she improved rapidly, and was up and about again. Desoxycorticosterone acetate was then given again, 20 mgm. daily. After nine days she complained of dryness of the mouth and malaise. The temperature rose to 100° F. Speech became slow and slurred. Blood-pressure 126/86. Blood-urea 25 mgm.%. She was at once given cortin, 30 c.c. daily, and her condition again improved quickly. Desoxycorticosterone was then given a third time, 40 mgm. daily. After three days only, the identical symptoms recurred; her temperature reached 103° F., and took four days to return to normal. Cortin was given again. Injections of desoxycorticosterone acetate gave rise to painful lumps in the buttock, which disappeared in four to five days. A large dose gave rise to a febrile reaction after a shorter interval than a small dose. But 20 c.c. cortin daily plus 4 c.c. sesame oil, intramuscularly for eight days and then 8 c.c. daily for three days, caused the same local reactions but there was no pyrexia. The sesame oil is not the cause of the pyrexia.

Case 2.—The second patient is a woman aged 41, under the care of Dr. Geoffrey Evans, to whom I am indebted for permission to describe the case.

One brother had died of pulmonary tuberculosis twenty-two years ago, one sister had had partial thyroidectomy for Graves' disease thirteen years ago, and had died from Addison's disease six years ago. The patient herself had had a partial thyroidectomy for Graves' disease twelve years previously. Another sister had a simple goitre and is still alive and well.

The patient gave a history of morning vomiting for one year and increasing lassitude for five months. Headache, retching, bouts of diarrhœa were troublesome symptoms, and darkening of the skin had been noticed for several months. She was deeply pigmented, and this was especially pronounced in the flexures and on pressure points and on the lips and inside the cheeks. Blood-pressure 100/60. serum sodium 315 mgm.%. Blood-urea 45 mgm.%.

Throughout her stay in hospital until her death she was an ill woman, suffering from almost incessant headache, much nausea, and retching, and vomiting almost every day. She was put on a low potassium diet, but seldom had solid food. Sodium was administered, 12 grm. of mixed sodium salts being given, but no matter how disguised, it invariable made her sick and some days was discontinued. Her intake of sodium was thus very inconstant. She was also given 5 mgm. daily of desoxycorticosterone acetate, but after nine days her condition had much deteriorated

and her temperature was raised. Cortin was begun, but in spite of 40–60 c.c. daily, the blood-pressure gradually fell to 80 mm. systolic, blood-urea to 60 mgm.%, and the pulse-rate to 150. Her condition was now critical. She was also given more intensive sodium treatment and also 40 mgm. desoxycorticosterone acetate daily and she made slight clinical improvement, but her improvement was much less than suggested by the chart of blood-urea and blood-pressure. After eleven days, she had a bout of high fever. Cortin was given again for two days, and then desoxy-corticosterone acetate. Again after four days she had a raised temperature and cortin, 40 c.c. daily, was therefore given, she became much brighter, but was still sick. The dosage was reduced to 20 c.c. daily and within a few days the blood-pressure fell rapidly and in three days suddenly dropped to 50 mm.Hg. She became comatose and intensive treatment with 160 c.c. cortin intravenously, and 40 grm. NaCl in hypertonic solution, failed to save her. At autopsy simple atrophy of the suprarenals was found. In this patient also desoxycorticosterone acetate appeared to be potent, but again febrile episodes occurred.

Summary

In these two cases desoxycorticosterone acetate was potent, but in both clinical relapse occurred, not typical of adrenal insufficiency, for the blood chemistry remained normal, and both cases showed febrile episodes. This may be due to a deficiency of some other essential constituent of adrenal extracts, or a toxic manifestation. In its present form desoxycorticosterone acetate does not seem to be a satisfactory substitute for cortin.

Dr. H. W. Dryerre said that he agreed with the former speakers as to the necessity for a high sodium chloride and low potassium intake in the diet, but whereas Drs. Simpson and Wilkinson suggested it was not necessary to continue the low potassium diet at home because of the difficulties of its preparation, he agreed with Dr. Himsworth that this should be carried out if possible. A low potassium diet might not be necessary, but it was essential that the patient should not have a high potassium diet. He did not insist on as low a potassium diet as suggested by Dr. Wilkinson, but was content if the daily intake did not exceed 1·5 grm. On discharge patients were given a list of recommended and forbidden edibles, and he did not consider a fixed diet necessary as long as the intake of sodium chloride was high and that of potassium low. He had found that a high potassium diet in cases of Addison's disease brought about an appreciable reduction in weight (and also incidentally a regression in the clinical condition) which was recovered from when the high potassium diet was stopped. If in addition to the high potassium diet cortin (Organon) was given, no appreciable difference occurred either in weight or clinical condition. In a case with no adrenal insufficiency the effect of high potassium was accompanied by an increase in weight probably as a result of the higher calorific value of such a diet. High potassium intake was detrimental in adrenal insufficiency, but its effect could be masked if sufficient cortin were given and further, a high sodium intake might also prevent the deleterious effects of high potassium.

He had not had the opportunity to try out desoxycorticosterone acetate as fully as the former speakers, but he had tried to obtain an objective estimate of its value by the use of a sodium excretion test modified from that of Cutler and co-workers, based on the fact that cases of adrenal insufficiency on a low sodium-high potassium diet show a high rate of urinary sodium and chloride excretion. He had found this to be the case for sodium, but his chloride figures were not diagnostic. He had also found blood estimations unreliable for diagnosis. In one case of advanced Addison's disease he had found the sodium excretion restored to normal after 10 mgm. of desoxy-corticosterone acetate were given daily, whereas previously the case had shown a high sodium excretion. He thought this test would be helpful in assessing the value of cortical extracts or synthetic substitutes, but his work on this matter was still in progress.

He had found the use of analgesics in cases of adrenal insufficiency sometimes accompanied by alarming consequences, more especially in the case of opiates whose use might be followed by a hypoglycæmic attack.

Section of the History of Medicine

President—A. P. Cawadias, O.B.E., M.D.

[*January* 11, 1939]

Allusions to a "Circulation" of the Blood in MSS. Anterior to *De motu cordis* 1628

By H. P. Bayon, M.D., Ph.D.

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The experimental, comparative anatomical and clinical observations by which William Harvey ascertained and demonstrated the circulation of the blood, proved of such signal importance in the subsequent development of biology and medicine, that anything connected with the inception of Harvey's doctrines deserves attention. I have recently come across several documents which bear on this topic.

The Canonici MSS. in the Bodleian comprise class notes of the lectures of Andrea Cesalpino at Pisa in 1590, and afford the solution of the question debated since Harvey's lifetime: whether Cesalpino anticipated Harvey's discovery.

The Rawlinson Collection of MSS. in the Bodleian includes a script alluding to a "Mr. Warrener" who was supposed to have accused Harvey of gross plagiary and to have said that he did not understand the motion of the heart.

The Birch Collection in the British Museum contains the writings of Walter Warren or Warner—the "Mr. Warrener" already mentioned—certain of which dealt with the function of the heart and the "circulatory or reciprocatory movement of the bloud".

I have compared these with the lecture notes by Harvey, his *Prelectiones* and his notes on *De musculis, motu localis etc.* and the notebooks of the physician Henry Power in the Sloane Collection of the British Museum.

The Canonici MSS. Notes of Cesalpino's 1590 Lectures at Pisa

These MSS. were originally collected from North Italian libraries by a Venetian Jesuit, Matteo Luigi Canonici (d. *c.* 1805) and then purchased by the Bodleian. That this collection contains the class notes of the lectures of Cesalpino in 1590 is particularly mentioned in *Bibliotheca Osleriana*.

There is no clue as to who may have been the writer of the Cesalpino lecture notes, but since they are in a clear, unhurried script and contain a feeling reference to Cesalpino's death in 1603, they are probably the fair copy of a previous manuscript by a pupil. The title page says: *Lectiones Andreae Caesalpini inceptae 3° Nov. 1590 Gymnasio Pisano.*

Andrea Cesalpino of Arezzo (1524–1603) studied medicine at Pisa from 1545 to 1549, when Realdo Colombo of Cremona (d. 1559) held the chair of anatomy there.

He graduated in 1551, became professor of medicine and botany in 1555, and in 1592 he was appointed physician to Pope Clement VIII (1592–1605) and performed the necropsy of S. Filippo Neri (d. 1595). Cesalpino was a copious writer on numerous subjects ; a thorough Aristotelian, he became renowned as a philosopher, naturalist (more particularly botanist), physician and demonologist. At one time his religious views were questioned, because he propounded the existence of a soul in the universe ; but Cesalpino was a clever dialectician and satisfied the Inquisition. His principal achievement is that of having arranged some 1,500 plants into groups according to their appearance, nature, and organs of fructification, rather than on the basis of their medical or other uses, as previously. Cesalpino's *De plantis* (Flor., 1583) is not illustrated, as distinct from the German Herbals ; his method of classification was followed by the anatomist Caspar Bauhin of Basel (1550–1624)[1] and the physician Robert Morison (1630–83) a correspondent of Harvey.

In 1655 and therefore during Harvey's lifetime, the " Florentine Æsculapius," Giovanni Nardi (d. 1655) had asserted in his *Noctes geniales* that Cesalpino had previously described the circulation of the blood. Nardi was a friend and correspondent of Harvey, but there is no reference to the matter in the existing letters to Nardi ; perhaps this question was not discussed. Since then it has been often stated in print that Cesalpino had discovered the circulation before Harvey, though Nardi's early criticisms have been overlooked by the authors I have been able to examine, *e.g.* De Renzi (1848), Ceradini (1876, 1906), Luciani (1926), Castiglioni (1936), and also Garrison (1929).

A statue was erected in 1877 to Cesalpino in Rome, with an inscription setting forth that he had discovered the circulation of the blood. Then the *Enciclopedia Italiana* (1931) records of him : *Dimostrò l'esistenza della circolazione pulmonare affermando etc.* This ignores that the pulmonal passage had been amply demonstrated by Realdo Colombo, probably already in his lectures in 1545, certainly in his anatomical treatise *De re anatomica* (Rome, 1559).

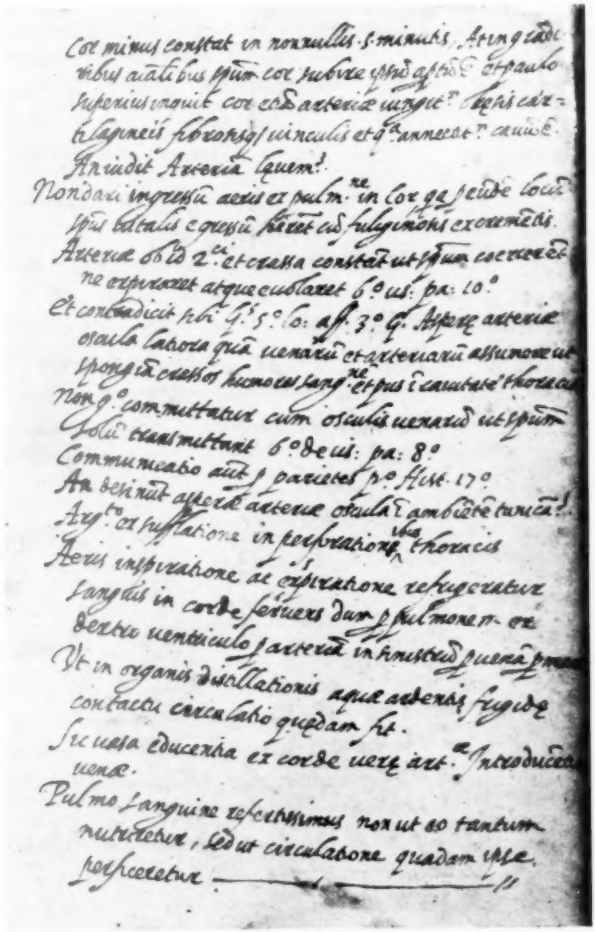
The present position of this controversy is that Cesalpino's writings contain many references to the *movement* of the blood and the *action* of the heart; but since these are not presented in a consequent manner, it has been easy to tear sentences from their context, and to suggest that Cesalpino was referring to the circulation as we know it. Nevertheless, a further examination of the text reveals that Cesalpino supported Aristotle's doctrine of the primacy of the heart and at the same time did not oppose Galen's opinion regarding the straining of the blood across the perforate interventricular septum of the heart ; moreover, though Cesalpino did employ the word *circulatio*, it seemed to have a different meaning to that it obtains nowadays in relation to the blood. These two important facts, that Colombo lectured on anatomy at Pisa in 1545, during Cesalpino's student days and that the word " circulation " in the latter's writings seemed to have a peculiar meaning, have been overlooked by authors, among whom Flourens (1854) can be quoted (p. 18) :—

" Enfin, Césalpin décrit à son tour, et sans citer Colombo (qu'il a surement point connu, puisque qu'il ne le cite point ; le grand mérite est toujour probe) la circulation pulmonaire ; et cette fois-ci, ce ne'est pas seulement la chose qui parait, c'est le mot."

Even if one must agree with Flourens' conviction that great merit is always transparently honest, if Cesalpino did not mention Colombo it was because he chose to ignore his existence. Harvey did not make any reference either to Cambridge or his teachers there ; in this case *le vrai mérite* preferred to be silent. It can be recalled that Ceradini (1876) was very indignant because Harvey had not quoted Cesalpino,

[1] Though Cesalpino's writings must have been known to Bauhin, in his anatomical treatises he does not allude to Cesalpino as having propounded the circulation of the blood, though Realdo Colombo is quoted.

but did not notice that Cesalpino neglected to mention Colombo's demonstration of the passage of the blood through the lung. I have discussed the question more fully in the *Annals of Science*, 1938–9; where I have been allowed to elucidate Colombo's significance as a true precursor of Harvey's experimental demonstrations; together



Class notes of Cesalpino's lectures at Pisa in 1590. (Canonici MS. from the Bodleian Library.)

with a discussion of the Galenical doctrine of the movement of the blood as it was understood in Harvey's time. In the same journal I referred to the remarkable allusions to a pulmonal passage of the blood in the lately translated MSS. of Ibn

an-Nafīs of Damascus (1210–88) which we owe to Meyerhoff (1935) and to Haddah and Khairallah (1936).

Here, therefore, attention can be restricted to the important passage in the Canonici MSS. which reveals how Cesalpino understood the movement of the blood and the action of the heart. This (p. 276) can be translated as follows :—

By inspiration and expiration of air, the blood of the seething heart is cooled during its passage through the lungs from the right ventricle by way of the artery into the left by way of the vein. In organs, as in distillation of alcohol, by contact with cold a certain circulation occurs.

This explains several allusions in the writings of Cesalpino, for example one occurring in Κατοπτρον (Francof., 1605 : first edition Rome, 1601) where he writes (Lib. VI, Ch. XIX, p. 473) :—

" *vt continuus quidam motus fieret ex venis in cor, & ex corde in arterias. Si quis autem contingat et motus contrarius, vt in animi perturbationibus membranatum positio obsisteret, ad tutelam caloris.*"

Thus Cesalpino understood the pulmonary circulation to be of the nature of a distillation by heat and explained the action of the valves of the heart as conserving the heat either of the blood or the heart, it is not quite clear which. He did not recognize the presence of valves in the veins, which had been already described by Fabrizio da Acquapendente in his lectures of 1574 and in print in 1603.

Since Walter Warren propounded similar views, we must consider whether the same interpretation could have been present in other minds about the same time. In the medical lexicon of Bartolomeo Castelli of Messina (d. 1607), first issued at Venice in 1607 and re-edited by Pancratius Bruno (1629–1709) at Nuremberg in 1682 and at subsequent dates, under the heading *Circulatio* we read :—

" *Circularis motus*, Gr. dici posset περίοδος, περιδρομὴ fortassis etiam κύκλωσις, ἢ περικύκλωσις frequentis usûs est in Medicinâ. Accipitur vero (1) Physice."

This physical circulation is instanced by the circulation of the blood as follows :—

" *Cujus circulus primus inventor & author praecipuus Guilielmus Harveus* " ; and it added " (2) Accipitur *chymicè vel Spagyricè*." The chemical or spagirical circulation is described ending with : " *Aquae circulatae meminit Paracel.* 1. 2. *de vir. membr. c.* 7. *Aquae vitae circulatae tr.* 2. *de membr. contract. c.* 3."

A little further on, the word *Circulatorium* is explained to mean a vessel in which a liquid ascending and descending " quasi *in circulo* rotatur ".

It can be said that these definitions not only explain Cesalpino's allusions, but those encountered in several authors, who stated that Paracelsus, among others, had described the circulation. A reference by Sir George Ent (1604–89) is in the second edition of his defence of Harvey *APOLOGIA | PRO | CIRCULATIONE | SANGUINIS | Qua respondetur | AEMYLIO PARISANO | Medico VENETO. | London* 1641. In the preface addressed to Harvey it is said : (f. A3).

Aiunt, rem eandem ab aliis, *Columbo* scil. & *Hofmanno*, prius excogitatam ; quae tamen, nisi fallor, illis nunquam in mentem venit, licet de sanguinis per pulmones transitu vera scripserint.

In the second edition, London, 1685, entitled : *APOLOGIA | PRO | Circuitione sanguinis*, a fuller statement is made as follows (Preface, f. B2 verso) :

Olaus|Borrichius ait Fridericum Bitiskium cre-dibile reddere | circulationem sanguinis Pa-racelso olim cognitam fuisse atque etiam cordis ἁιματοποίησιν. . . . *Alii dicunt rem eandem á Columbo,*[2] *Spigelio atque + Hofmanno aliisque prius excogitam fuisse : Neque Andream Cesalpinum eti-amsi motui sanguinis, e dextro ventriculo per pulmonis in sinistrum Circulationis no-men indidit, quicquam amplius sensisse arbitror.*

[2] It will be noted that Ent had then heard of further assumed precursors of Harvey.

The lecture notes in the Bodleian confirm that Cesalpino in his writings referred to the pulmonary passage of the blood according to the description made by the Pisan anatomist Realdo Colombo and showed that Cesalpino understood the much-discussed term *Circulatio* in a manner differing from that demonstrated by Harvey in relation to the whole volume of the blood.

Allusion in the Rawlinson Collection to "Mr. Warrener"

Readers of John Aubrey's *Lives of Eminent Men* (and the companion volume *Brief Lives etc.*) will recall that Dr. Pell said that Walter Warner had reasoned demonstratively by the beats of the pulse that there was a circulation of the blood. Reference is then made to a letter of Izaak Walton (1593–1683), dated 2. Dec. 1680 :—

My Lord of Winchester tells me he knew him [Walter Warner] *and that he said that he first found out the circulation of the blood and discovered it* [to] *Do. Harvie (who said it was he [himself] who found it) for which he is so memorably famose.*"

Aubrey is generally admitted to be an unreliable witness, but similar remarks were made by Anthony à Wood (1632–1695) who wrote in *Athenae Oxonienses* (London, 1691–2 Col. 391) :

He (I mean *Warner*) also did make it appear (*m*) in a MS of his composition that the blood in a body did circulate, which he communicating to the immortal *Harvey* he took his first hint thence concerning that matter which he afterwards published as the first inventor.

(*m*) so used to say *Dr. G. Morley* [3] sometimes B. of Winton and *Dr. Joh. Pell.*[4]

Thus presented, the evidence seems to weigh heavily against Harvey. Rolleston (1873) mentioned that in the Bodleian there was an anonymous biographical miscellany, the Rawlinson Collection (B. 158) which on pp. 152–3 related that Henry, Earl of Northumberland [5], being imprisoned in the Tower, had some learned persons to converse with, who were dubbed his "Three Magi". I have examined these interesting MSS. and found the following § on page 152–3 :

" Another was Mr. Warrener the Inventor probably of the circulation of the blood,—of which Subject he made a treatise, consisting of two books which he sent to Dr. Harvey, who Epitomized and printed them [*p.* 153] in his own name ; he usually said that Dr. Harvey did not understand the motion of the Heart, which was a perfect Hydraulick. Sir Thomas Ailesbury Master of requests & a great Officer in the Mint, told me that he had Warrener's book and that I should have it, but coming to London he found his Library, wherein were many rare and curious books, plundered and amongst the rest taken away. Dr. Pain that very Ingenious and Learned Canon of Christ Church, told me he had seen & pervied this book of Warreners."

Walter Warren's MSS. in the British Museum's Birch Collection

Professor George Rolleston of Oxford traced in the British Museum a MS. of 416 folio pages ascribed to Warren, and since 36 pages referred to the circulation or reciprocation of the blood, it is reasonable to admit that they represent the text of

[3] George Morley (1597–1684) D.D. Oxford, 1642 ; Dean of Christ Church. Bishop of Winchester.

[4] John Pell (1611–1685) D.D. Lambeth ; mathematician ; M.A. Trinity College, Cambridge ; Rector of Mildenhall ; one of Cromwell's diplomatists ; a friend of Comenius.

[5] This was Henry Percy, IX. Earl of Northumberland, named the "Wizard Earl" (1564–1632). He was imprisoned in 1606, but a large library was placed in his cell, mainly Italian books, incl. Tasso and Machiavelli. His Three Magi were : Thomas Hariot (1560–1621) mathematician, geographer and astronomer ; Robert Hues or Hughes (1553–1632) B.A. Oxon, geographer ; and Walter Warner. The Earl also dined with Sir Walter Raleigh (1552–1618). He was freed 18 July 1621 and left in a carriage drawn by eight horses.

the treatise in two volumes to which reference has been made. Rolleston then gave excerpts from these writings in the Oration of 1873 and mentioned that Mr. E. M. Thompson of the British Museum considered that paper and writing dated the script about the year 1610. I should feel inclined to date it later, particularly as no paper in the same volume is earlier than 1635, though this is not definite evidence ; but the style of writing seems to indicate a later date.

The text consists of a spun out discourse in which the formation of the world or macrocosmos is discussed. Then the problem of the circulation is approached and the movement of the blood, action of the heart and the resemblance to distillation considered ; the capillaries are mentioned as *funicular canallets of the sanguiducts*. There follows a long disquisition on the " circulatory or reciprocatory motion of the blood " ; but the two words are not interchangeable, for they mean different movements : one in a circle, the other one to and fro ; the latter describing the ancient or Galenical doctrine of the movement of the two separate types of blood.

Notwithstanding the long and tedious treatment of the subject the meaning is quite clear : " the blood circulates by the pulsifick innate heat of the heart ", the valves helping to stop a movement in the contrary direction. It was, however, recognized that this "hydraulick" motion had to be subjected to the structure of the " hart ", which was muscular and acted like a muscle. It is remarkable that it had been noted that the excised heart continued to beat for a good time out of the body.

A full quotation will give an impression of the peculiar language with which these ideas are clothed ; e.g. pp. 132–3 :—

p. 132.—*For the determining thereof there are but these two generall cases possible or imaginable that is the principiū passium must necessarily be subiected ether in the bloud itself or in the organs continent namely the hart or the vessels annexed and continued thereto. If the principiu passivm be in the bloud it can not be conceded to be any other thing then that property of rarefactibility by heat and recondensability by cold or refrigeration before mentioned.* [page 133] *thereof and in the vaines and arteries to retaine the state of condensation. Wch way hath been more particularly examined in the former discussions.*

So far I have been unable to trace any detailed information about Walter Warren, except that he edited Hariot's *Artis analyticae praxis* etc. (London, 1631) and died in 1640.

[Dr. Charles Singer, who kindly edited this paper for the *Proceedings*, called my attention to a passage in one of Boyle's works, first published in 1663, which mentions Mr. Warner. I have obtained the quotation from the second edition, Oxford, 1664, entitled : SOME CONSIDERATIONS / Touching the / USEFULNESSE OF EXPERIMENTAL / Natural Philosophy.

The relevant passage is as follows : Page 34. Thus the Circuiar motion of the Blood, and structure of the Valves of the Heart and Veins (The consideration thereof, as himselfe told me, first hinted the Circulation to our Famous *Harvey*) though [*page* 35] now Modern Experiments have for the main (the Modus seeming not yet so fully explicated) convinc'd us of them, we acknowledge them to be very expedient, and can admire God's Wisdome in contriving them : Yet those many Learned Anatomists, that have for so many succeeding Ages preceded both Dr. *Harvey* and *Columbus*, *Caesalpinus*, *Padre Paulo*, and Mr. *Warner*), for each of these four last are suppos'd by some to have had some notion of the Circulation) by all their deligent contemplation of humane bodies, never dream'd (for ought appears) of so advantagious an use of the Valves of the Heart, nor that nimble Circulative Motion of the Blood, of which our modern Circulators think they discern such excellent Use, not to say, Necessity.]

Canon Isaac Voss (1618–1689)

The Birch Collection in the British Museum consists of several volumes containing MSS. by several authors, such as Pell and Warren who have already been mentioned, and also Isaac Voss (Vossius) Canon of Windsor from 1673 till his death. Voss edited Pliny's *Natural History* 1669 and wrote against Cartesianism, 1662–3. Charles II made the characteristic remark that Voss would believe anything, if it were not in the Bible! Voss in his *Variarum observationum* (London, 1685, p. 71) stated that the circulation of the blood had been known to the Chinese for 4,000 years; that it had been recorded in writing by Cesalpino, and then by Sarpi, who convinced a certain Englishman, *Anglo quidem*, who wrote it down in two books, which he later suppressed, for they met with no approval; but that some years afterwards, Harvey treated the same argument with more success.

The merits of Cesalpino as a naturalist have been admitted, and it has been shown that he could not have described the circulation of the blood, as we understand it, for he had only added the conception of a chemical circulation caused by heat, to the demonstrations of the lung passage by Colombo. The case of Paolo Sarpi (1552–1623) a broadminded monk and theologian, a correspondent of William Gilbert and Francis Bacon, has often been considered. In none of his many writings is there any definite mention of either the valves in the veins or a circulatory movement of the blood. If Voss had Walter Warner in mind as the *Anglo quidem*, then nothing could be easier than to tear single sentences from their context and to prove that Warner had a clear conception of the circulation of the blood; but the fuller excerpts I have been able to reproduce show that his notions were not only foggy, but referred to a chemical circulation, not the circulation as it occurs in the blood system of man and warm-blooded animals.

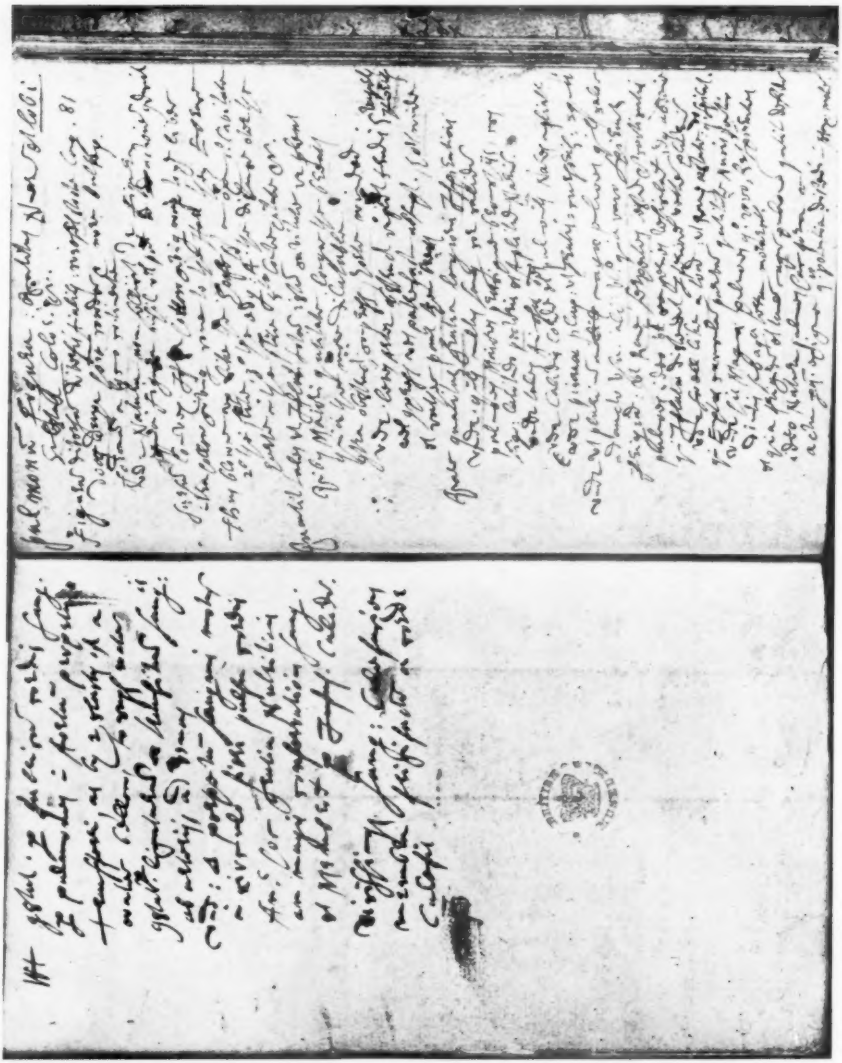
The *Prelectiones* of William Harvey

These notes in Harvey's handwriting are those on which he based his Lumleian lectures from 1616 onwards. They are at present bound in a small volume and were originally in the Library of the physician Sir Hans Sloane (1660–1752)—the foremost "toyman" of his time—and then transferred in 1754 to what later became the British Museum.

In 1873 when George Rolleston tried to trace them, they had been mislaid; but were later discovered among the printed books by Sir Edward Henry Sieveking (1816–1904) who described them in the Oration of 1877. These notes reveal Harvey's mind with a transparency not obtainable from his printed works.

The *Prelectiones* contain f. 80 VERSO the often republished statement which has been deciphered as follows:—

WH c/stat p fabrica cordis sang.
per pulmones in Aorta perpetuo
transferri, as by 2 *clacks of a*
water bellow to rays water *is*
c/stat p ligatura transitu sang:
ab arteriis ad venas
Und ∆ *perpetu sanguinis motu*
in circulo fieri pulsu cordis
An ? hoc gratia nutritionis
an magis conservationis sang.
et membm p infus calid
vicissim sang calefaciens
membra frigifacta a corde
Calefit



Two pages from Harvey's "Prelectiones" in the British Museum : f. 80 verso shows a thicker, darker writing than previous or subsequent pages.

The meaning is clear to those who have read *De motu* ; the structure of the heart perpetually moves the blood like a pump with two clacks or valves ; by means of ligature the transit of blood from arteries to the veins can be proved as well as the continuous circle of the blood movement and causation of the pulse. Why ? for the purpose of nourishing or better conservation of the blood, warming the limbs by perfusion or alternatively warming cold limbs from the warm heart.

It is particularly noticeable how Harvey, who had obtained a clear conception of the nature of the circulation of the blood, was able to give a coherent account of it, even by means of a disjointed scribble. Those who read Cesalpino may obtain the impression that he was trying to cloud with words the description of a process that was still very unclear in his mind.

Reverting to the actual script itself, Underhill (1905) was the first to suggest that this note might possibly be a later addition, perhaps by interleaving. Accordingly the Librarian of the New York Academy of Medicine, Dr. Archibald Malloch, wrote to the Keeper of the MSS. in the British Museum, Mr. J. P. Gilson, who replied that there was no external evidence showing that this folio 80 was not a direct continuation of what preceded. This is correct, for both the paper and writing of f. 80 RECTO are clearly a continuation of the previous pages, and the characteristic spidery writing is unquestionably by the same hand. Nevertheless f. 80 VERSO is definitely a later addition on the reverse of a leaf that had already been written on. It had possibly been left blank for the purpose ; perhaps because when Harvey had written the previous chapter, he was not quite sure of his facts. The f. 80 VERSO, containing the statement about the circulation, was written by the same hand employing a blunter quill and different, darker ink to the recto ; then f. 81 v. continued in the same brown, thin, filigree writing.

This most important section is thus a later addition, though it cannot be ascertained how much later. It may be that Harvey mentioned the matter tentatively in his first lectures and added the note later. Still it is noteworthy that in the preface of *De motu cordis* 1628 addressed to the President of the College of Physicians, John Argent (1573–1643), Harvey states that he had confirmed the circulation in his presence by many ocular demonstrations during " more " than nine years. All depends upon the interpretation to be placed on " more " ; three years added to nine gives twelve and brings us to the year 1616. If so, it is not clear why Harvey did not say twelve at once ; for it is understood that Dr. Argent was present at *all* lectures.

This all shows how easily misunderstandings can arise. Mr. Gilson gathered that f. 80 was meant, and without troubling about *recto* and *verso*, stated quite rightly that the paper and writing were the same as the preceding. Had he turned the page he would have immediately noticed the difference.

THE PHYSICIAN HENRY POWER (1623–D. 23. DEC. 1668)

Henry Power entered Christ's College, Cambridge 15. Dec. 1641, became a B.A. in 1644 ; M.D. 1655 ; F.R.S. 1. July 1663 and corresponded with Sir Thomas Browne (1605–1682), practised medicine in Halifax and then at New Hall near Ealand. He was the author of the first English book on microscopy, entitled *Experimental Philosophy in three books etc.* (London, 1664). Thomas Cowles (1930) mentions Power's poem on the microscope of which line 21 says :—

" *There yow may see the pulsing Heart, driue on The Blood in it's due Circulation.*"

Power who died young in 1668 did not contribute to the *Philosophical Transactions*, which began in 1665, but he left behind numerous MSS. many of which are in the

Sloane Collection at the British Museum and reveal the full extent of his inquiring mind. One little bound volume N. 1343 is mainly concerned with experiments demonstrating the circulation of the blood. This was written in 1652, therefore during Harvey's lifetime and contains the remarkable entry on top of. f. 97 :—

Circutatio sanguinis Harveiana Inventa ab Authore An. Dom. 1614. Other entries are *Inventio aselliana de venis lacteis & de motu chyli anno* 1622 and later on *Inventio Wirsungiana* 1642.

These dates refer to published works ; so that for Harvey the corresponding date should be 1628, the date of publication of *De motu cordis*, unless Power had reasons for choosing another date. It will be seen that 1614 antedates the Lumleian lecture by two years, and unless it is a *lapsus calami* for 1616, Power must have been in a position to decide on the first recognition of the circulation by Harvey. The MSS. of Power are interesting since they prove how Harvey's example directly incited biological experimentation in inquisitive minds.

Harvey probably knew Warner and had possibly read some of his writings and for this reason may have referred to the necessity of proving the circulation "*per αὐτοψία non mentis agitatio*".

The Londoner William Fitzer, the Frankfurt Publisher of *De motu cordis* 1628

It has often been asked why Harvey should have sent the script of his first book to be printed in Frankfurt ; to say that it was the centre of the book trade is not a satisfactory reply, for a book printed in England would have sold as well. Malloch (1929) p. 99 pointed out that William Fitzer also published several of Robert Fludd's (1574–1637) books and it is known that Fludd was well acquainted with Harvey. In the *Annals of Science* 1938 I was able to show that Fludd was the first author to approve of Harvey's doctrine of the circulation in print (*PVLSVS* &c. Francof. 1631). Brief biographical notes on Fludd were included in a paper in these *Proceedings* 1938, **32**, 31–42. Fulton (1937) has found that Sir Kenelm Digby (1603–1665) in his *Two Treatises* (Paris, 1644) wrote the first appreciation of Harvey's doctrine to appear in English.

In William Foster's *HOPLOCRISMA | SPONGUS : | or | A Sponge to wipe away | the Weapon-salve.* &c. (London, 1631), Robert Fludd's advocacy of the sympathetic weapon-salve was attacked, not because it was useless, but because it savoured of magic so that it could not be lawful for an honest and religious man to use it. It may be mentioned that both Digby and van Helmont were convinced believers in the efficacy of the salve. Among other arguments Foster said that Fludd's books were printed beyond the Seas ; (p. 37). In : *Doctor* FLVDDS *Answer vnto* M. FOSTER / OR, / THE SQVESING OF / Parson FOSTERS SPONGE, ordained / *by him for the wiping away of the* / WEAPON-SALVE &c. &c. (London, 1631.) on p. 22 it was replied that the books were printed abroad, because the printers paid for his script, instead of charging for the printing. Similar reasons may have decided Harvey to entrust his book to Fitzer, who was a publisher, not a licensed printer, of whom only eight were allowed in Frankfurt at the time.

In May last year, Dr. Archibald Malloch of New York informed me that he was preparing some notes on William Fitzer and kindly gave me a valuable reference, a paper by Moritz Sondheim in *PHILOBIBLON* 1933 VI 9–34 from which I learnt that William was the son of Thomas Fitzer of London, was born *c.* 1600, obtained the freedom of the Stationers' Company on 12. May 1624, married Susanna, daughter

of Johann Theodor de Bry (1561–1623) on 17. April 1625; after many unfortunate vicissitudes, William Fitzer died in Heidelberg, 21. May 1671. It is interesting to note that Theodor de Bry (1528–1598) printed in 1590 a French edition *A report of the New found land of Virginia* by Thomas Hariot, to whom reference has been made. In the British Museum there is a volume, lately in the Sion College Library, bearing the imprint: *Apud GVILIELMVM FITZERVM, Anglum* which is a copy of the *OPERA MEDICA* (Francofurti, 1629) by Nicholas-Abraham La Framboisière (1557–? 1640). Fitzer appears to have been interested in "Spagyrics" and may have taken part in the Rosicrucian movement; Fludd was also very favourably disposed towards Rosicrucian doctrines, though probably not a professed Rosicrucian.

Summary

I.—The class notes of Cesalpino's 1590 Pisa lectures in the Bodleian confirm that he described the passage of the blood across the lungs like Realdo Colombo, who had taught anatomy at Pisa during the former's student days and whose *De re anatomica* 1559 was a popular textbook.

II.—These notes reveal that Cesalpino understood the circulation of the blood to consist in what was then known as a *chemical circulation*, i.e. similar to that occurring in a still and therefore consisting in an alternate rising and falling of fluid, caused by the heat of the heart. The valves served to preserve the heat.

III.—This interpretation makes Cesalpino's allusions to a "circulation" of the blood understandable, because otherwise they appeared to be confused and contradictory.

IV.—References in Aubrey, Anthony à Wood, Vossius and the Rawlinson Collection to a treatise describing the circulation of the blood, which had been copied or plagiarized by Harvey, led to a re-examination of the Birch Collection in the British Museum, which does contain a MS. by Walter Warren containing such allusions.

V.—The Warren MS. may either be a copy of an earlier draft or else its date seems later than that assigned by Mr. E. M. Thompson, viz. 1610. It also discusses a chemical circulation, refers to the mechanical action of the heart and its action when excised from the body, but cannot be said to bring any concrete proof of the circulation in the sense it was demonstrated by Harvey.

VI.—From the original of Harvey's *Prelectiones* in the British Museum it is not ascertainable whether he described and demonstrated the circulation already in 1616, because f. 80 VERSO is clearly a separate, possibly later addition. In the preface of *De motu cordis* 1628 Harvey wrote that the circulation had been demonstrated in the presence of Dr. Argent, "nine or more years" previously.

VII.—A note in the MSS. of Henry Power (1623–1668) dates the "invention" of the circulation by Harvey in 1614. This may indicate the first inception of the doctrine which was then publicly demonstrated shortly after 1616.

VIII.—Whether Harvey mentioned his views on the circulation fourteen, twelve, or only nine years before the publication of *De motu* 1628, it still remains most remarkable that such a striking new doctrine induced no reaction among its hearers and that no allusion was made to it in print. After 1628 the first favourable notice in print was that of Robert Fludd in 1631; in English that of Sir Kenelm Digby in 1644.

IX.—It seems reasonable to suggest that Harvey, at the instigation of his friend Robert Fludd, sent *De motu cordis* to the Englishman William Fitzer in Frankfurt, son-in-law of Theodor de Bry who had already printed several of Fludd's works.

REFERENCES

The controversy regarding Cesalpino and Harvey having lasted nearly three centuries, the relative literature is extensive; it is contained in the works of Willis (1878) Dalton (1884) D'Arcy Power (1897) Malloch (1929) so that it need not be listed here, but the book by Izquierdo deserves special notice: HARVEY, *Iniciador del Metodo Experimental* (Mexico, 1936). It quotes and discusses the several Italian and Spanish authors who have propounded the claims of the various precursors of Harvey. Reference has been made to the help obtainable from *Bibliotheca Osleriana* (Oxford, 1929). I wish particularly to acknowledge the courtesy of the Trustees of the British Museum, the Bodleian Library, Oxford, and the University Library, Cambridge, in supplying me with photographs, photostats and aiding the search for manuscripts and printed works.

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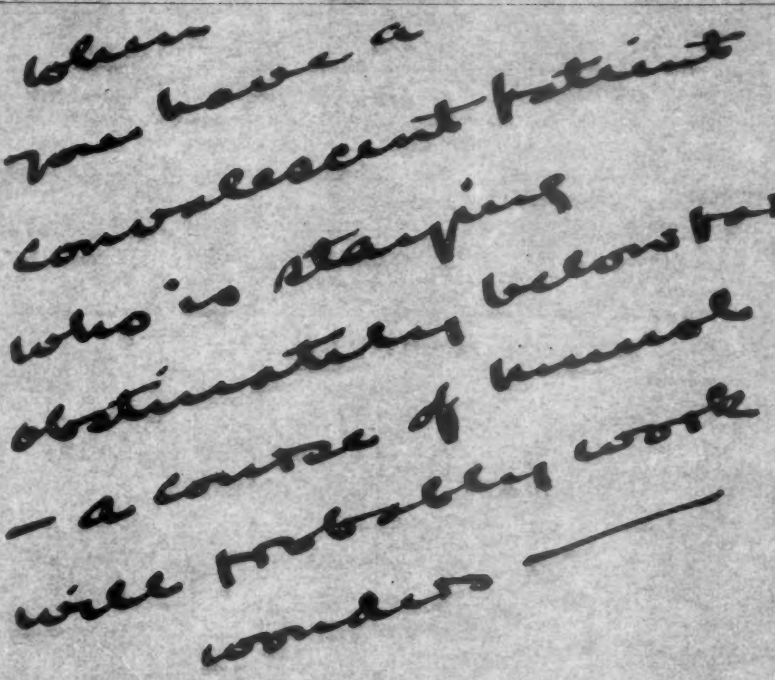

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